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EFFECT OF DIHYDROTACHYSTEROL IN TREATMENT OF PARATHYROID DEFICIENCY

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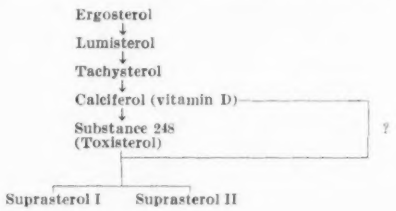
Tachysterol is one of several sterols derived from ergosterol by irradiation with ultraviolet light. Its relation to the other sterols can best be illustrated by the scheme modified by Bills [1] from that of Setz:



Experimentally tachysterol has been found to cause an increase in absorption and urinary excretion of calcium, and a rise in the concentration of calcium in the serum. There is no evidence that parathyroid function is affected. An orally effective derivative, dihydrotachysterol (antitetanic preparation no. 10, or "A. T. 10"), was first used in the treatment of parathyroid tetany by Holtz,[2] in Germany, in 1933. Since then it has been extensively used, chiefly in Germany, and its effects have been reported on in considerable detail. The literature has recently been reviewed by Albright and his associates.[3] From

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1. Bills, C. E.: The Chemistry of Vitamin D, J. A. M. A. **110**:2150 (June 25) 1938.

2. Holtz, F.: Die Behandlung der postoperativen Tetanie, Arch. f. klin. Chir. **177**:32, 1933.

3. Albright, F.; Bloomberg, E.; Drake, T., and Sulkowitch, H. W.: A Comparison of the Effects of A. T. 10 (Dihydrotachysterol) and Vitamin D on Calcium and Phosphorus Metabolism in Hypoparathyroidism, J. Clin. Investigation **17**:317, 1938.

their review the principal data concerning dihydrotachysterol may be summarized.

Most writers agree that dihydrotachysterol has no antirachitic effect. The chief effects noted have been increase in the concentration of serum calcium and decrease in the concentration of inorganic serum phosphorus. The urinary calcium has been found to be increased and the fecal calcium decreased. Both the ionized and the protein-bound fraction of the serum calcium have been reported to be increased, with a more marked effect on the ionized fraction in cases of tetany. Holtz, Gissel and Rossmann [4] concluded that the calcium bound by protein was the first to become increased, with a subsequent increase in the diffusible fraction. (Their conclusions, however, do not appear to be tenable, for reasons which will be referred to later.) If the calcium intake is low, the increase in serum calcium is effected by withdrawal of calcium from the skeletal stores. No detailed studies of the effect of dihydrotachysterol on calcium and phosphorus metabolism appear to have been made prior to those reported by Albright and his associates.[3] They compared the effects of vitamin D, dihydrotachysterol and parathyroid extract (solution of parathyroid) in 3 cases of hypoparathyroidism and concluded that the fundamental actions of vitamin D and dihydrotachysterol are similar: an increased absorption of calcium from the intestine and an increased excretion of phosphorus in the urine, the ratio of the latter to the former being greater with dihydrotachysterol. They concluded that the effect of dihydrotachysterol on the concentrations of calcium and phosphorus in the serum is secondary to these fundamental actions. Their observations indicate that the action of vitamin D is slower in onset and more prolonged than that of dihydrotachysterol.

Excessive doses of dihydrotachysterol may produce fatal intoxication with hypercalcemia and extensive calcification, especially in the urinary tract, where calculi may occur. The preparation used clinically is a 0.5 per cent solution of dihydrotachysterol in sesame oil. It is administered orally. The optimal dose varies widely, depending on the severity of symptoms and the degree of hypocalcemia. An initial dose of 5 to 10 cc. daily for three or four days usually results in a marked rise in concentration of serum calcium in from three to nine days after the first dose is given—much larger doses are occasionally necessary, however. The maintenance dose is usually between 2 and 6 cc. weekly in cases of mild involvement. There is a cumulative effect, and periodic determinations of the serum calcium are essential to avoid dangerous hypercalcemia. There is no evidence of harmful effect from prolonged administration of the substance in proper doses. The requirement is increased during menstruation, pregnancy and periods of great physical

4. Holtz, F.; Gissel, H., and Rossmann, E.: Experimentelle und klinische Studien zur Behandlung der postoperativen Tetanie mit A. T. 10, Deutsche Ztschr. f. Chir. **242**:521, 1934.

or emotional activity. Castration by roentgen irradiation is said to decrease the requirement in women. The action of dihydrotachysterol is said to be antagonized by estrogen and androgen. Lenticular cataract, a common complication of parathyroid deficiency, is said to be prevented by dihydrotachysterol but not to be affected once it has begun.

Dihydrotachysterol has been shown to be highly effective in controlling and preventing the manifestations of parathyroid deficiency, a large number of cases in which it was successfully used having been reported, chiefly in the German literature.[5] MacBryde,[6] Arnold and Blum [7] and Swinton [8] have recently reported on its use in the United States. It has also been used in the management of a number of other conditions —the tetany of sprue, asthma, urticaria, hemophilia, impetigo herpetiformis and a variety of peripheral circulatory disturbances. At present the chief advantages of the drug in treating parathyroid tetany appear to be (1) its prompt and continued efficacy by peroral administration in maintaining normal concentrations of serum calcium and controlling symptoms without the necessity of dietary restriction (low phosphorus diet) or adjuvant therapy (calcium or vitamin D), and (2) the small maintenance dose usually necessary. The principal objections to its use appear to be (1) its cost and (2) the necessity of guarding against hypercalcemia.

We wish to report the effects of dihydrotachysterol on 5 patients with parathyroid deficiency following thyroidectomy and ranging from five months to thirteen years in duration. The method of study in general followed the plan described by Bauer and Aub.[9] The patients were given a diet the calcium content of which was approximately 1 Gm. daily. All rejected food was weighed and the calcium content calculated.

The total period of study was divided into periods of three days as follows: (*a*) two to four periods during which the patient continued to receive the medication previously necessary to control symptoms (one of our patients, M. R., had received no previous therapy); (*b*) two

5. Symposium: Die Tetanie (Nebenschilddrüseninsuffizienz) und ihre Behandlung, Med. Klin. **32**:656, 1936. Martini, P., and Heymer, A.: Beitrag zur Behandlung der postoperativen Tetanie mit dem antitetanischen Präparat 10 (A. T. 10-Holtz), München. med. Wchnschr. **80**:1864, 1933. Winterstein, O.: Zur Behandlung schwerer und leichter Tetanien mit A. T. 10, Deutsche med. Wchnschr. **60**:1831, 1934.

6. MacBryde, C. M.: The Treatment of Parathyroid Tetany with Dihydrotachysterol, J. A. M. A. **111**:304 (July 23) 1938.

7. Arnold, C. H., and Blum, H.: The Control of Hypoparathyroidism, West. J. Surg. **44**:546, 1936.

8. Swinton, N. W.: Postoperative Parathyroid Tetany, New England J. Med. **217**:165, 1937.

9. Bauer, W., and Aub, J. C.: Studies of Inorganic Salt Metabolism: I. The Ward Routine and Methods, J. Am. Dietet. A. **3**:106, 1927.

periods during which all medication was omitted; (*c*) one period during which dihydrotachysterol was given alone in doses of 10 cc. daily, and (*d*) one to five periods during which dihydrotachysterol was given alone in doses of 2 cc. daily. One patient (L. H.) received viosterol alone in doses of 2 cc. daily for two periods prior to the administration of dihydrotachysterol. A greater number of control periods without calcium or viosterol therapy would have been desirable (except in the case of M. R., who had received no such therapy). However, the 4 patients who had received this therapy had such severe parathyroprival symptoms that they could not safely be carried longer than for two periods (six days) without treatment. All urine and feces were collected for each period, the limit of the periods for collection of feces being determined by the appearance of carmine in the stools.

Determinations at the end of each period were made of the following: the total of serum calcium, by the method of Clark and Collip;[10] the diffusible fraction of serum calcium, from ultrafiltrates of serum obtained through collodion sacks according to a modification of the method of Greenberg and Gunther;[11] the inorganic phosphorus of the serum, by the method of Fiske and Subbarow;[12] the total serum protein, and the calcium contents of the urine and feces, which were pooled for each period. The calcium of the urine and that of the feces were measured by modifications of the methods of Shohl and Pedley[13] and McCrudden,[14] respectively.

REPORT OF CASES

CASE 1.—L. H., an unmarried white woman aged 44, underwent a subtotal thyroidectomy for hyperthyroidism in another hospital in 1923. This was followed by bilateral paralysis of the recurrent laryngeal nerves, necessitating a tracheotomy, and by severe symptoms of parathyroid deficiency. The patient was first seen by us in 1927, at which time bilateral lenticular opacities were found. There has been little change in these. The patient has been under continuous observation since 1927. Two parathyroid transplants were made in 1928,

10. Clark, E. P., and Collip, J. B.: The Tisdall Method for Determination of Blood Serum Calcium, with a Suggested Modification, J. Biol. Chem. **63**:461, 1925.

11. Greenberg, D. M., and Gunther, L.: On the Determination of Diffusible and Nondiffusible Serum Calcium, J. Biol. Chem. **85**:491, 1930.

12. Fiske, C. H., and Subbarow, Y.: The Colorimetric Determination of Phosphorus, J. Biol. Chem. **66**:375, 1925.

13. Shohl, A. T., and Pedley, F. G.: A Rapid and Accurate Method for Calcium in the Urine, J. Biol. Chem. **50**:527, 1922.

14. McCrudden, F. H.: The Quantitative Separation of Calcium and Magnesium in the Presence of Phosphates and Small Amounts of Iron, Devised Especially for the Analysis of Foods, Urine and Feces, J. Biol. Chem. **7**:83, 1909; The Determination of Calcium in the Presence of Magnesium and Phosphates; the Determination of Calcium in the Urine, ibid. **10**:187, 1911.

with little benefit. Therapy had included large doses of calcium, vitamin D, parathyroid extract (solution of parathyroid), desiccated thyroid and a diet low in phosphorus. The patient had become anemic, and electrocardiographic evidence of myocardial damage had appeared. Dihydrotachysterol was given from March 27 to Sept. 17, 1937, with resulting improvement. From September 17 to November 8, she received 15 teaspoonfuls of calcium lactate and 10 minims (0.62 cm.) of viosterol daily with a low phosphorus intake. Her symptoms were only partially controlled by this therapy. She was under observation in the hospital from November 8 to December 9, 1937. Since that time she has remained under observation in the outpatient clinic and has been kept fairly comfortable by large doses of calcium lactate combined with small doses of dihydrotachysterol (adequate doses of the latter were not possible because of the cost). The potency of dihydrotachysterol is illustrated by the fact that the patient showed severe symptoms of intoxication

TABLE 1.—*Record of Patient L. H.*

Date	Total Calcium, Mg. per Cc.	Diffusible Calcium, Mg. per Cc.	Inorganic Phosphorus, Mg. per Cc.	Serum Protein, Gm. per Cc.	Comment
11/12/37	8.4	...	4.4	7.2	Calcium lactate and viosterol
11/20/37	5.7	2.7	5.0	5.6	Viosterol only for 5 days; marked symptoms of parathyroid deficiency
11/23/37	5.8	...	...	...	All medication withdrawn; severe symptoms
11/26/37	5.3	2.5	5.7	5.4	
11/29/37	6.4	...	...	...	Dihydrotachysterol begun 11/27/37 (10 cc. daily)
12/ 2/37	8.4	3.8	4.9	6.0	Marked clinical improvement; 34 cc. dihydrotachysterol to date
12/ 6/37	9.2	4.3	4.0	5.9	Dihydrotachysterol, 2 cc. daily
12/ 9/37	8.6	...	...	...	Dihydrotachysterol, 2 cc. every other day; left hospital
12/20/37	8.9	...	...	...	Dihydrotachysterol, 2 cc. every other day
1/ 5/38	8.3	...	...	...	
1/21/38	7.8	...	...	...	Calcium lactate added
4/29/38	10.2	...	...	...	
7/12/38	15.7	...	3.1	...	Severe symptoms of hypercalcemia
9/15/38	9.8	...	3.9	...	1 cc. dihydrotachysterol every other day; 10 teaspoonfuls calcium lactate daily; low phosphorus diet; no tetany, but some miscellaneous symptoms

(vertigo, tinnitus, thirst, polyuria, nausea and abdominal cramps), with a rise of total serum calcium to 15.7 mg. per hundred cubic centimeters, after taking 8 teaspoonfuls of calcium lactate and 2 cc. of dihydrotachysterol daily from June 12 to July 8. The significant data relating to this patient are shown in table 1.

CASE 2.—J. J., a married mulatto woman aged 38, underwent a subtotal thyroidectomy for hyperthyroidism in another hospital in 1927. Severe symptoms of parathyroid deficiency, including convulsive seizures, began several months later and continued intermittently until we first saw the patient, in 1935. At this time there was evidence of mild recurrent hyperthyroidism and bilateral cataracts. There was a questionable history of syphilitic choroiditis. Since first entering this clinic, the patient had received calcium lactate, viosterol, parathyroid extract, a low phosphorus diet and intermittent iodine therapy. At the time of admission to the hospital she was taking 16 teaspoonfuls of calcium lactate and 10 minims of viosterol daily, with only partial relief of symptoms. She was studied in the hospital from Sept. 8 to 30, 1937. Subsequently she was under observation in

the outpatient clinic. Dihydrotachysterol was omitted from Jan. 14 to Oct. 13, 1938, because she could not afford it. During this period her general condition was about as it was before dihydrotachysterol therapy was started, and a convulsion occurred in September, despite a diet low in phosphorus and administration of 15 teaspoonfuls of calcium lactate daily. After the resumption of dihydrotachysterol the symptoms disappeared within four days, and the total serum calcium rose to a normal level. The cataracts progressed. The significant data relating to this case are shown in table 2.

CASE 3.—H. E., a white man aged 40, underwent a partial thyroidectomy for nontoxic nodular goiter in another hospital in 1918. This was followed immediately by parathyroid tetany, which was manifested by intermittent syncopal attacks or convulsive seizures until the patient was first seen by us, in April 1937.

TABLE 2.—*Record of Patient J. J.*

Date	Total Calcium, Mg. per Cc.	Diffusible Calcium, Mg. per Cc.	Inorganic Phosphorus, Mg. per Cc.	Serum Protein, Gm. per Cc.	Comment
9/13/37	8.3	4.3	3.9	7.5	Viosterol and calcium lactate
9/17/37	6.5	...	...	...	Therapy stopped 9/15/37; severe tetany
9/20/37	5.6	2.6	5.0	7.1	Symptoms increasingly severe
9/21/37	5.5	...	...	...	Dihydrotachysterol 9/21 to 9/24/37 (10 cc. daily)
9/24/37	6.4	...	...	...	Clinical improvement; dihydrotachysterol, 2 cc. daily
9/26/37	9.2	3.7	4.2	7.7	No symptoms
9/29/37	9.4	4.4	4.0	7.1	Discharged 9/30/37; dihydrotachysterol reduced to 2 cc. twice weekly; unrestricted diet
10/ 9/37	9.3	...	...	...	
11/26/37	8.0	...	...	...	Minimal symptoms; dihydrotachysterol, 2 cc. twice weekly
12/15/37	7.6	...	...	...	Dihydrotachysterol increased to 3 cc. twice weekly 11/30/37; discontinued 1/14/38
3/21/38	9.1	...	...	...	
4/19/38	7.7	...	...	...	
9/20/38	8.2	...	3.8	...	Convulsion 9/21/38; symptoms only partially controlled
10/17/38	9.7	...	4.0	...	On 10/13 1 cc. dihydrotachysterol every other day added to 10 teaspoonfuls of calcium lactate daily; no symptoms at time of writing

At this time the concentration of calcium was 5.6 mg. and that of inorganic phosphorus 5.5 mg. per hundred cubic centimeters of serum. There was no evidence of lenticular cataract. The symptoms were partially controlled by 6 teaspoonfuls of calcium gluconate daily. The patient was under observation in the hospital from Dec. 6 to 26, 1937. Since that time he has been followed in the outpatient clinic. He has remained free from symptoms, although the concentration of serum calcium has remained slightly below the normal level with 2 cc. of dihydrotachysterol twice a week and no other medication or restriction of diet. The significant data relating to this case are shown in table 3.

CASE 4.—M. H., a married white woman aged 30, underwent a partial thyroidectomy for nontoxic nodular goiter in another hospital in 1935. Symptoms of parathyroid deficiency developed immediately, with occasional convulsions. There was also evidence of hypothyroidism. Therapy had included small doses of calcium lactate, parathyroid extract (solution of parathyroid) and desiccated thyroid. She was first seen by us on Feb. 4, 1938, when the concentration of serum calcium was 7.5 mg. per hundred cubic centimeters. She was under observation in

the hospital from February 7 to March 5. A parathyroid transplant was made on March 18; subsequent observations indicated that this was without effect. The patient has remained under observation in the outpatient clinic since leaving the hospital. She has remained free from symptoms and without evidence of cataract

TABLE 3.—*Record of Patient H. E.*

Date	Total Calcium, Mg. per Cc.	Diffusible Calcium, Mg. per Cc.	Inorganic Phosphorus, Mg. per Cc.	Serum Protein, Gm. per Cc.	Comment
12/13/37	7.8	3.2	5.5	7.1	Calcium lactate
12/16/37	6.9	...	...	...	Calcium withdrawn 12/14/37
12/20/37	6.8	3.0	5.9	7.6	
12/22/37	7.7	...	...	...	Dihydrotachysterol started (10 cc. daily for 3 days, thereafter 2 cc. daily); mild symptoms of parathyroid deficiency
12/25/37	10.3	4.0	4.9	7.3	No symptoms; discharged 12/26/37
1/21/38	9.0	...	4.5	...	No symptoms; 2 cc. dihydrotachysterol twice weekly
2/ 4/38	9.4	...	4.7	...	No symptoms; 2 cc. dihydrotachysterol twice weekly
3/18/38	8.5	...	4.0	...	No symptoms; 2 cc. dihydrotachysterol twice weekly
4/20/38	8.3	...	4.7	...	No symptoms; 2 cc. dihydrotachysterol twice weekly
7/15/38	8.6	...	...	...	No symptoms; 2 cc. dihydrotachysterol twice weekly
10/28/38	7.4	...	4.4	...	Dihydrotachysterol omitted for 2 weeks, then resumed for 4 days prior to determination; no symptoms

TABLE 4.—*Record of Patient M. H.*

Date	Total Calcium, Mg. per Cc.	Diffusible Calcium, Mg. per Cc.	Inorganic Phosphorus, Mg. per Cc.	Serum Protein, Gm. per Cc.	Comment
2/13/38	7.5	3.2	4.8	6.8	Tetany of moderate severity; calcium lactate plus viosterol
2/16/38	6.2	...	...	...	Tetany more marked; no medication
2/19/38	5.7	2.6	5.5	6.5	Tetany; no medication
2/22/38	7.0	...	...	...	10 cc. dihydrotachysterol daily 2/20 to 2/23/38
2/25/38	9.5	4.2	3.7	6.9	2 cc. dihydrotachysterol daily 2/23 to 2/27/38; marked improvement
3/ 3/38	9.1	...	4.1	...	2 cc. dihydrotachysterol every other day 2/27 to 3/5/38; left hospital 3/5/38
5/10/38	8.9	...	3.4	...	2 cc. dihydrotachysterol 3 times a week; no symptoms
6/11/38	9.1	...	3.8	...	2 cc. dihydrotachysterol 3 times a week
6/24/38	7.5	...	4.5	...	Dihydrotachysterol stopped 6/11/38; recurrence of symptoms
7/22/38	8.5	...	3.5	...	Dihydrotachysterol resumed (2 cc. twice a week) 7/1/38
10/14/38	10.1	...	3.5	...	No symptoms; 2 cc. dihydrotachysterol twice weekly

under treatment with 2 cc. of dihydrotachysterol two or three times a week. This medication was stopped from June 11 to July 4 to permit evaluation of the parathyroid transplant; there were a fall in the concentration of serum calcium and recurrence of symptoms at this time. The significant data relating to this case are shown in table 4.

CASE 5.—M. R., a married white woman aged 30, was first seen in the outpatient clinic in July 1937, at which time a diagnosis of toxic diffuse goiter was

made. A subtotal thyroidectomy was done in this hospital on August 20. The postoperative convalescence was without incident. The patient was not seen by us after her discharge until Jan. 5, 1938, when she presented evidence of parathyroid deficiency; the concentration of serum calcium at this time was 6.3 mg. per hundred cubic centimeters. She was studied in the hospital from January 14 to February 11. She has received no dihydrotachysterol since leaving the hospital but has continued on a low phosphorus diet, with varying doses of desiccated thyroid and calcium lactate. At the time of writing (November 1938) the concentration of serum calcium was normal (9 mg. per hundred cubic centimeters), three weeks after calcium lactate was stopped. The significant data relating to this case are shown in table 5.

COMMENT

Our experience confirms the previous reports of the effectiveness of dihydrotachysterol in relieving the symptoms of parathyroid deficiency

TABLE 5.—*Record of Patient M. R.*

Date	Total Calcium, Mg. per Cc.	Diffusible Calcium, Mg. per Cc.	Inorganic Phosphorus, Mg. per Cc.	Serum Protein, Gm. per Cc.	Comment
1/18/38	6.1	2.3	6.7	7.5	No therapy; moderate symptoms of tetany
1/21/38	6.0	...	6.7	...	No therapy; moderate symptoms of tetany
1/24/38	6.5	...	...	...	10 cc. dihydrotachysterol daily 1/22 to 1/24/38
1/27/38	7.6	...	6.1	7.1	2 cc. dihydrotachysterol daily 1/25 to 2/8/38; gradual improvement in symptoms
1/30/38	7.8	3.4	6.4	7.2	2 cc. dihydrotachysterol daily
2/ 2/38	8.4	...	...	...	2 cc. dihydrotachysterol daily
2/ 5/38	8.6	3.7	5.8	7.4	2 cc. dihydrotachysterol daily
2/ 8/38	8.7	...	...	...	Dihydrotachysterol stopped
2/ 9/38	9.0	3.4	5.4	7.7	Almost no symptoms; left hospital 2/11/38
11/ 8/38	10.6	...	4.2	...	No dihydrotachysterol since 2/11/38; no calcium since 10/4/38; no evidence of tetany

and increasing the concentration of serum calcium. The danger of producing toxic symptoms and hypercalcemia is indicated by our experience with patient L. H. It should be emphasized again that the severity of symptoms in 4 of our patients precluded the possibility of longer periods of observation without therapy. In 4 of our patients the response to dihydrotachysterol was relatively prompt; the concentration of total serum calcium returned to normal, with corresponding relief of symptoms, in from four to nine days after the beginning of treatment. The fifth patient (M. R.) had received no previous treatment and presented relatively mild symptoms; she showed a slow, progressive increase in concentration of serum calcium, with corresponding gradual clinical improvement, over a period of eighteen days during which she received doses of dihydrotachysterol identical with those given the other patients.

Our experience also confirms previous observations as to the lack of correlation between the degree of hypocalcemia and the severity of symptoms. The case of patient H. E. illustrates this fact particularly; his symptoms, which were largely episodic, were often absent when the concentration of serum calcium was decreased (7.4 mg. per hundred cubic centimeters). Patient J. J., on the other hand, had a generalized convulsion the day after the concentration of serum calcium was determined to be 8.2 mg. per hundred cubic centimeters.

In table 6 are given the results of the fractionations of the serum calcium. The total calcium in the serum was calculated in terms of millimols per kilogram of water by means of the conversion factors

TABLE 6.—*Summary of Studies of Serum Calcium*

Subject	Date	Specific Gravity, 20 C./20 C.	Total Calcium, mM/Kg. H_2O	Diffusible Calcium, mM/Kg. H_2O	Ca^{++} (Calculated), mM/Kg. H_2O	Nondiffusible Calcium, mM/Kg. H_2O	Diffusible Calcium-Ca^{++} Ratio	Diffusible Calcium-Total Calcium Ratio
J. J.	9/10	1.0287	2.22	1.08	1.00	1.14	1.08	0.49
	9/20	1.0276	1.49	0.65	0.61	0.84	1.07	0.44
	9/26	1.0294	2.47	0.93	1.00	1.54	0.93	0.38
	9/29	1.0277	2.51	1.11	1.10	1.40	1.00	0.44
L. H.	11/14	1.0279	2.25	....	0.97	....	....	....
	11/20	1.0232	1.51	0.68	0.65	0.83	1.05	0.45
	11/26	1.0228	1.40	0.63	0.70	0.77	0.90	0.45
	12/2	1.0245	2.23	0.95	1.09	1.28	0.97	0.43
	12/6	1.0241	2.44	1.08	1.20	1.36	0.90	0.44
H. E.	12/13	1.0276	2.09	0.80	0.90	1.19	0.89	0.38
	12/20	1.0291	1.82	0.75	0.74	1.07	1.01	0.41
	12/25	1.0282	2.75	1.00	1.20	1.75	0.87	0.36
M. R.	1/18	1.0288	1.63	0.58	0.66	1.05	0.88	0.36
	1/27	1.0286	2.04	....	0.89	....	....	....
	1/30	1.0281	2.09	0.85	0.90	1.24	0.94	0.41
	2/5	1.0285	2.30	0.93	0.97	1.37	0.96	0.40
	2/9	1.0293	2.42	0.85	1.00	1.57	0.85	0.35
M. H.	2/13	1.0269	2.00	0.80	0.88	1.20	0.91	0.40
	2/19	1.0260	1.52	0.65	0.67	0.87	0.97	0.43
	2/25	1.0272	2.54	1.05	1.13	1.49	0.93	0.41

obtained from measurements of specific gravity.[15] The diffusible calcium in the ultrafiltrate was calculated in terms of millimols per kilogram of water, the average room temperature being assumed to be 22.5 C. and the presence of other solids being disregarded. Calculations then were made for the concentration of calcium ions from the concentration of serum protein and total calcium according to the relation derived by McLean and Hastings.[16] It will be seen in the table that within the limits of error of the method the ratio of the diffusible calcium to the calculated calcium ions is 0.95 ± 0.02 (standard error). It is of

15. Sunderman, F. W.: Studies on Serum Electrolytes: X. The Water of Serum, J. Biol. Chem. **113**:111, 1936.

16. McLean, F. C., and Hastings, A. B.: The State of Calcium in the Fluids of the Body: Conditions Affecting the Ionization of Calcium, J. Biol. Chem. **108**:285, 1935.

especial interest to note that the ratio of diffusible calcium to total calcium is fairly constant for each person. There is no evidence to suggest that either the diffusible or the nondiffusible portion of the serum calcium is selectively affected by dihydrotachysterol. This observation is at variance with the conclusions of Holtz, Gissel and Rossmann,[4] who stated that under the action of dihydrotachysterol the "colloidal" (nondiffusible) fraction was the first to increase and that later an increase occurred in the calcium of the ultrafiltrate. These authors failed to calculate the concentration of serum calcium on a water basis and obtained their figure for "colloidal" calcium by subtracting the value for the diffusible fraction from that for the total calcium. They furnished no data concerning serum protein, total solids

TABLE 7.—*Summary of Studies of Calcium Balance*

Subject	Number of Three Day Periods	Therapy	Average Intake for Period, Gm.	Average Urinary Calcium for Period, Gm.	Average Fecal Calcium for Period, Gm.	Average Calcium Balance for Period, Gm.
J. J.	2	Viosterol; calcium	16.50	0.65	15.70	+0.15
	2	None	0.90	0.38	1.43	—0.91
	3	Dihydrotachysterol	0.90	0.44	0.71	—0.25
L. H.	2	Viosterol; calcium	17.24	0.97	15.23	+1.04
	2	Viosterol (only)	2.44	0.19	2.11	—0.14
	2	None	2.70	0.11	2.65	—0.06
	4	Dihydrotachysterol	2.70	0.54	2.77	—0.51
M. H.	2	Viosterol; calcium	7.99	0.42	7.76	—0.19
	2	None	3.28	0.20	2.05	+0.94
	2	Dihydrotachysterol	3.33	1.20	1.69	+0.44
H. E.	2	Viosterol; calcium	9.26	0.20	8.02	+1.04
	2	None	3.41	0.12	3.38	—0.09
	2	Dihydrotachysterol	3.35	0.75	2.15	+0.45
M. R.	2	None	2.65	0.65	0.79	+1.21
	6	Dihydrotachysterol	2.71	0.63	0.54	+1.54

or specific gravity from which values for nondiffusible calcium may be recalculated on a water basis. We are unable to confirm their results. Within the limits of error of our method, it appears that there is no evidence of the presence of diffusible nonionized calcium in the serum in significant amounts.

In general, an inverse relation was observed between the concentration of total calcium and that of inorganic phosphorus in the serum. When the concentration of serum calcium returned to normal levels after the administration of effective amounts of dihydrotachysterol, the concentration of inorganic phosphorus also tended to return to the normal range.

In table 7 are summarized the data relating to calcium balance in our patients. It will be seen that the average fecal calcium was less during the periods of dihydrotachysterol therapy than in the control periods without any therapy in 4 of the 5 patients. It will also be seen that urinary excretion of calcium was greater during the periods of dihydrotachysterol therapy than in the control periods without therapy in 4 of

the 5 patients. These data, so far as they permit conclusions, tend to support previous observations that dihydrotachysterol leads to increased urinary excretion of calcium at the expense of fecal calcium.

SUMMARY

Observations are reported on 5 patients with parathyroid deficiency following thyroidectomy who were treated with dihydrotachysterol. These observations included determinations of calcium balance, total and diffusible serum calcium, serum protein and inorganic serum phosphorus before and during the administration of dihydrotachysterol.

Dihydrotachysterol is highly effective in increasing the concentration of serum calcium and in relieving the symptoms of parathyroid deficiency.

In excessive doses it is capable of producing hypercalcemia with toxic symptoms.

The diffusible and the nondiffusible fraction of the serum calcium share about equally in the rise in concentration of total serum calcium which follows the administration of dihydrotachysterol.

Insofar as the data permit conclusions, the trend of changes in the urinary and the fecal calcium in our cases supports previous opinion that dihydrotachysterol increases urinary excretion of calcium at the expense of fecal calcium.

Part of the dihydrotachysterol used was donated by the Winthrop Chemical Co., Inc., New York.

EVALUATION OF SULFANILAMIDE IN THE TREATMENT OF PATIENTS WITH SUBACUTE BACTERIAL ENDOCARDITIS

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Sulfanilamide (paraaminobenzenesulfonamide) is effective in the treatment of infections due to beta hemolytic streptococci. Clinical and experimental observations indicate that this chemotherapeutic agent may be of value in the treatment of infections caused by the less virulent classes of streptococci. The hemolytic streptococci designated as the alpha group include Streptococcus viridans. Bliss, Long and Feinstone [1] observed that the growth of forty-two of forty-five strains of alpha hemolytic streptococci was inhibited by a 1:10,000 concentration of the drug.[2] Long and Bliss [3] found that sulfanilamide exerted a definite bacteriostatic effect in urine cultures of alpha streptococci. It would be desirable to ascertain the effect of sulfanilamide on the lesions of animals infected with the less virulent groups of streptococci, but such infections are not easily produced. Muether and Kinsella [4] stated that they established bacterial endocarditis with persistent bacteremia in dogs, using a culture of nonhemolytic streptococci. After daily oral administrations of sulfanilamide, 4 of 5 dogs made a complete recovery

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Read in part at a meeting of the Minnesota Society of Internal Medicine, June 4, 1938.

From the Department of Medicine, University Hospitals, University of Minnesota Medical School.

1. Bliss, E. A.; Long, P. H., and Feinstone, W. H.: The Differentiation of Streptococci and Its Relation to Sulfanilamide Therapy, South. M. J. **31**: 303 (March) 1938.

2. Dr. Perrin Long informed us that these 45 strains of alpha streptococci were isolated from 45 patients with subacute bacterial endocarditis. The 3 strains for which sulfanilamide was not bacteriostatic were Str. viridans, but belonged to the enterococcus group, as do about 10 to 15 per cent of the viridans strains which are recovered from the blood of patients with subacute bacterial endocarditis.

3. Long, P. H., and Bliss, E. A.: Observations upon the Mode of Action and the Clinical Use of Sulfanilamide in Urinary Tract Infections, South. M. J. **31**: 308 (March) 1938.

4. Muether, R. O., and Kinsella, R. A.: Sulfanilamide in the Treatment of Experimental Endocarditis, J. A. M. A. **110**:603 (Feb. 19) 1938.

from the infection. In a discussion of these results, Muether expressed the opinion that sulfanilamide is of no value in the treatment of subacute bacterial endocarditis in man.

There are few available data in the literature concerning the results of sulfanilamide therapy in patients with infections due to Str. viridans. At the Johns Hopkins Hospital [1] 2 patients with infections of the soft tissues responded quickly to sulfanilamide, and 2 patients with infections of the urinary tract made prompt recoveries. Love [5] has reported a case of meningitis due to a gram-negative nonhemolytic streptococcus which responded favorably to sulfanilamide and prontosil.[6]

The etiologic agent in subacute bacterial endocarditis is usually Str. viridans. There is considerable uncertainty as to whether sulfanilamide is of any value in this disease. Bliss, Long and Feinstone [1] treated 3 patients with massive doses of the drug, with the result that cultures of the blood remained sterile, but the course of the disease was not altered. Klee and Römer [7] administered prontosil [8] to 5 patients with subacute bacterial endocarditis, with no beneficial results. On the other hand, Hussey [9] reported in detail a case of bacterial endocarditis in which the patient was apparently cured by sulfanilamide. The causative organism in his case was a beta hemolytic streptococcus. More recently, Major and Leger [10] have recorded in detail a case of subacute bacterial endocarditis with Str. viridans as the etiologic agent. They stated that recovery followed the use of prontosil,[6] but that the patient died of heart failure twenty-nine days after the temperature had become normal and twelve days after prontosil [6] had been discontinued. A microscopic section of the aortic valve, obtained at autopsy, showed clumps of gram-positive diplococci deep beneath the healed surface. Cultures of material from excised portions of the mitral and aortic valves were sterile.

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5. Love, J. W.: Nonhemolytic Streptococcus Meningitis: Report of a Case Successfully Treated with Sulfanilamide and Prontosil, J. Lab. & Clin. Med. **23**:482 (Feb.) 1938.

6. The preparation used was disodium 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′,6′-disulfonate. This is now known as neoprontosil.

7. Klee, P., and Römer, H.: Prontosil bei Streptokokkenerkrankungen, Deutsche med. Wchnschr. **61**:235 (Feb. 15) 1935.

8. The formula is not given in the report. The preparation used was probably the original prontosil (4-sulfamido-2′,4′-diaminoazobenzene hydrochloride), a compound that has been little used in this country.

9. Hussey, H. H.: Probable Bacterial Endocarditis Apparently Cured with Sulfanilamide: Report of a Case, M. Ann. District of Columbia **6**:275 (Sept.) 1937.

10. Major, R. H., and Leger, L. H.: Recovery from Subacute Infectious Endocarditis Following Prontosil Therapy, J. A. M. A. **111**:1919 (Nov. 19) 1938.

Our interest in treating several patients with subacute bacterial endocarditis with sulfanilamide was the result of a sequence of events observed in 2 patients (cases 1 and 2) which followed administration of the drug, and of the paucity of detailed clinical studies available in the literature. In initiating this study, we were fully aware of the nature of the endocardial lesion in this disease. Before the introduction of sulfanilamide, Swift [11] stated the problem of therapy for subacute bacterial endocarditis as follows:

> When one recognizes that the vegetations are thick masses of material in which the bacteria are actively growing, and that many of the bacterial agglomerations are situated at a considerable distance from any circulating blood, it is difficult to understand how any therapeutic agent introduced into the blood stream can have a completely effective bactericidal action throughout the entire extent of the vegetation.

We also recognized that there is an accumulating body of evidence [12] that patients with subacute bacterial endocarditis may occasionally recover from the disease. In the event of such an outcome in a well established case there might be a considerable temptation to ascribe the result to the use of certain therapeutic agents.

METHOD OF STUDY

During the past year 12 patients with subacute bacterial endocarditis have been treated with sulfanilamide. While a correct diagnosis of this disease is attended with difficulty, we relied principally on (1) the history; (2) the presence of an organic cardiac murmur, which changed in intensity from time to time; (3) the manifestations of embolic phenomena, and (4) the demonstration of persistent bacteremia. Though instances of subacute bacterial endocarditis without bacteremia do occur,[13] we recovered organisms repeatedly from the blood of all 12 patients. The patients included 10 females and 2 males. Their ages varied between 18 and 70 years. Six patients, all females, had a congenital cardiac lesion. Three had a patent ductus arteriosus; 2 had a patent interventricular septum; and 1 had coarctation of the aorta with a bicuspid aortic valve. There were 4 patients with rheumatic heart disease. Three had mitral stenosis, and a fourth had an aortic lesion in addition to

11. Swift, H. F.: Subacute Bacterial Endocarditis, in Nelson Loose-Leaf Living Medicine, New York, Thomas Nelson & Sons, 1937, vol. 4, p. 323.

12. Libman, E.: A Further Report of Recovery and Recurrence in Subacute Bacterial Endocarditis, Tr. A. Am. Physicians **48**:44, 1933. Weiss, S., and Rhoads, C. P.: Healing and Healed Vegetative (Subacute Bacterial) Endocarditis, New England J. Med. **199**:70 (July 12) 1928. Hamman, L.: Healed Bacterial Endocarditis, Ann. Int. Med. **11**:175 (July) 1937.

13. Keefer, C. S.: Subacute Bacterial Endocarditis: Active Cases Without Bacteremia, Ann. Int. Med. **11**:714 (Nov.) 1937.

mitral stenosis. One elderly patient had aortic stenosis thought to be due to arteriosclerosis, but while he was under observation a persistent diastolic murmur became audible over the aortic area. One patient had bacterial vegetations on an otherwise normal cardiac valve, the condition being demonstrated at autopsy. The etiologic agent was Str. viridans in 11 cases and Staphylococcus albus in 1. All eleven strains of Str. viridans showed the typical green type of hemolysis when streaked out on blood agar plates and when studied by the pour plate technic. Veal infusion agar with a p_H of 7.4 to 7.6 was used throughout this study. Sulfanilamide was given orally, whenever possible, in daily divided doses totaling between 45 and 100 grains (2.91 and 6.48 Gm.). As a precautionary measure against the development of acidosis, 5 to 15 grains (0.32 to 0.97 Gm.) of sodium bicarbonate was given orally with each dose of sulfanilamide.

REPORT OF CASES

CASE 1.—E. L., a 35 year old white woman, was admitted to the hospital on March 27, 1937. She was in good health until seven months before entry, when she noticed unusual fatigue, weakness, fever and chills. Her appetite was poor, and she noted a progressive loss of weight. The symptoms continued unabated until admission to the hospital. There was no history of rheumatic fever or of chorea, and she had no knowledge of an organic cardiac lesion prior to her present illness.

Physical examination showed that the patient was emaciated and poorly developed and appeared chronically ill. The skin of the face and arms exhibited a diffuse brownish pigmentation. There were no petechiae on the mucous membranes of the eyes or mouth. The lungs were normal. The blood pressure was 88 mm. of mercury systolic and 56 mm. diastolic. On percussion the heart was found to be enlarged to the left. The apical impulse was prominent. A diastolic thrill was palpable at the apex. On auscultation over the apex an early systolic thrill following the first sound was detected. The second sound was obscured by a high-pitched diastolic murmur. The pulmonic second sound was accentuated. The cardiac rhythm was regular. The spleen was firm and slightly tender and was palpable 3 cm. below the costal margin. The liver was not felt. No peripheral edema was present.

Laboratory examination showed that the value for hemoglobin was 57 per cent (16.5 Gm. per hundred cubic centimeters, equivalent to 100 per cent [Sahli [14]]), for erythrocytes 2,600,000 per cubic millimeter and for leukocytes 4,900 per cubic millimeter. Examination of the urine revealed numerous leukocytes in the sediment. Serologic tests of the blood for syphilis gave negative results. A culture of the blood taken on each of four successive days yielded Staph. albus, with 4 to 11 colonies per cubic centimeter of blood.

The patient was given 4 Gm. of sulfanilamide a day by mouth. Within a few days there was a marked decrease in her temperature (fig. 1), and she felt considerably improved. It is of interest, in the light of subsequent findings, that a teleroentgenogram taken at this time showed a heart shadow with both right and left ventricular enlargement. The esophagus was slightly displaced posteriorly in the region of the left atrium.

14. This value was used throughout our studies.

On the seventeenth day after admission the patient's condition became suddenly worse. She was drowsy and responded only to painful stimuli. The pupils were dilated, and definite rigidity of the neck was noted. The reflexes were hypoactive but equal. A lumbar puncture showed the pressure of the spinal fluid to be 24 mm. of mercury. The fluid was cloudy and contained 350 cells per cubic millimeter, 75 per cent of which were polymorphonuclear neutrophils and 25 per cent lymphocytes. The value for total protein was 151.6 mg. per hundred cubic centimeters. Smears and cultures of the fluid showed Staph. albus on several occasions. The blood culture at this time yielded the same organism. For seven days the patient was given a total of 4 Gm. of sulfanilamide a day. This was

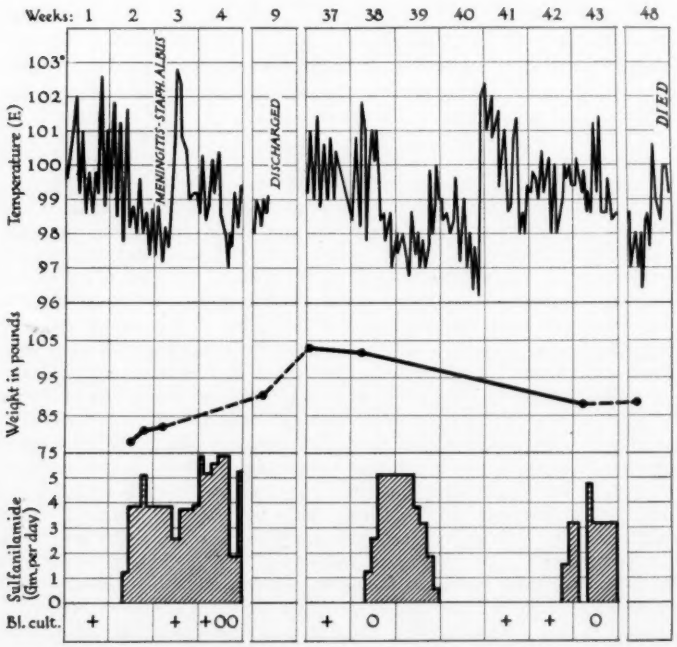

Chart 1.—Subacute bacterial endocarditis and meningitis due to Staph. albus (case 1). After the administration of sulfanilamide the patient became afebrile and gained weight, and the blood cultures were sterile.

administered subcutaneously and intrathecally. Her condition improved rapidly. By the twenty-sixth day of hospitalization her temperature was normal. In the meantime, cultures of the blood and spinal fluid were sterile. The patient's weight on admission to the hospital was 80 pounds (36.3 Kg.), and when she was discharged, on June 24, she weighed 91 pounds (41.3 Kg.). The cardiac findings remained essentially the same.

She returned home and was able to assume her household activities. In August 1937 her weight was 120 pounds (54.4 Kg.), representing a gain of 40

pounds (18.1 Kg.). She was instructed to take her temperature three times a day, and at no time did she have fever, until December 15, when she contracted an infection of the upper respiratory tract. Because the fever persisted, she was advised to enter the hospital on Jan. 4, 1938. There was an increase in cardiac dulness as compared with the finding in the previous examination. A systolic and a diastolic thrill were present over the apex. Harsh systolic and diastolic murmurs were heard over the same area. On auscultation the lungs were found to be clear. The liver was just palpable, and the spleen was felt 2 cm. below the costal border. There was no peripheral edema. The value for hemoglobin was 70 per cent. The blood count showed 3,400,000 erythrocytes and 8,700 leukocytes per cubic millimeter. The urine contained a trace of albumin, and there were many leukocytes in the sediment. Staph. albus was persistently present in several blood cultures. A teleroentgenogram and an esophogram showed a definite displacement of the esophagus to the right and posteriorly in the region of the left auricle.

During the first nine days after admission she was febrile in the afternoon. On the tenth day sulfanilamide therapy was again instituted. After this her temperature returned to normal and blood cultures were sterile. After sulfanilamide had been given for one week, marked anorexia developed. The drug was then given subcutaneously as an 0.8 per cent solution in physiologic solution of sodium chloride, but the anorexia continued, with nausea and vomiting. Sulfanilamide therapy was then discontinued. The patient continued to have anorexia, though the nausea and vomiting abated. On the twenty-sixth day of hospitalization signs of cardiac failure appeared for the first time. There was edema of the face and extremities. There was evidence of pulmonary congestion. The liver was now palpable 6 cm. below the costal margin and was tender. After the use of diuretics the signs of congestive heart failure diminished. The temperature became elevated, and Staph. albus was isolated from the blood cultures. Sulfanilamide was given subcutaneously, and again the temperature became normal and the blood cultures sterile. The nausea and vomiting returned, however, and no further attempts were made to give sulfanilamide. The signs of cardiac decompensation returned and became progressively more marked. The patient died on March 25.

Autopsy was done by Dr. Robert Hebbel. The heart weighed 360 Gm. The epicardium and myocardium appeared normal. The valvular abnormalities were limited to the mitral valve. There were multiple small, reddish, friable vegetations on its auricular surface, most of which were at some distance from the free margin. The vegetations were more numerous above the posterior than above the anterior leaflets. There were a few scattered vegetations through the wall of the left auricle. A few vegetations were observed on the ventricular surface of the anterior mitral leaflets, near the line of closure. Staph. albus was cultured from the vegetations. The leaflets were not thickened. There was slight atherosclerosis of the coronary vessels.

The spinal cord was exposed and appeared normal. A stained section of the thoracic portion of the spinal cord, examined microscopically, showed no abnormality.

The pathologic diagnosis was: subacute bacterial endocarditis; congestive heart failure; infarcts of the lungs and kidneys; thrombosis of the right pulmonary artery; bronchopneumonia, and subacute splenitis.

The clinical course of the second patient (case 2) merits a detailed description because when first seen she presented a definite clinical picture of severe subacute bacterial endocarditis. She has been free of

any evidence of infection for nine months after her discharge from the hospital.

CASE 2.—B. G., an 18 year old white girl, single, entered the hospital on Sept. 27, 1937. All her life she had had dyspnea on exertion. She had never been cyanotic. Seven months before admission she became increasingly weak and observed pallor of her features. Five months later she had a sudden onset of pain in the right lower quadrant of the abdomen and the left side of the chest. Her temperature was 103 F. She had a cough productive of blood-tinged sputum. These symptoms subsided in a week, but left her feeling tired and listless. Prior to admission, she had been confined to bed for three weeks. At this time she noted "blood blisters" over the skin of the lower extremities. These ruptured and became crusted. Two weeks before admission she had several tarry stools. She felt drowsy and had severe headaches. Edema of the ankles was observed. She had lost 20 pounds (9.1 Kg.) in weight over a period of four months. The menses had been regular until one year before her present illness, but since then had been scanty and irregular. She had never had rheumatic fever, chorea or scarlet fever.

Physical examination revealed an apathetic, undernourished girl with a peculiar yellowish pallor. There was no icterus of the scleras. Cyanosis was not present. There were no petechiae of the mucous membranes of the scleras and mouth. The lungs were normal. The heart did not appear enlarged on percussion. The blood pressure was 112 mm. of mercury systolic and 60 mm. diastolic. The heart sounds were distant and regular. There was a systolic murmur over the pulmonic area which radiated to the left clavicle, and at times a faint diastolic murmur was heard in the same region. A blowing systolic murmur was heard at the apex. The liver was palpated 5 cm. below the costal margin and was tender and soft. The spleen was tender and soft and was felt 2 cm. below the costal margin. There was edema of the lower parts of the legs. Numerous small reddish brown pigmented areas were present in the skin of the lower extremities, which were the sites of the previously mentioned "blood blisters."

Examination of the urine showed albuminuria on two occasions, and there were numerous erythrocytes in the sediment. The value for hemoglobin on admission was 30 per cent; there were 1,600,000 erythrocytes per cubic millimeter. The leukocytes numbered 6,200 per cubic millimeter. Occasional reticuloendothelial cells were seen in stained blood films. The value for the total plasma proteins was 6.7 Gm. per hundred cubic centimeters. The sedimentation rate was 97 mm. in one hour (Westergren). Str. viridans was obtained several times from cultures of the blood. Colony counts showed 30 colonies per cubic centimeter on one occasion and 200 colonies on another. The stools did not contain occult blood.

A teleroentgenogram taken shortly after entry was interpreted as showing questionable enlargement of the left ventricle and an area of either consolidation or infarction of the lower left pulmonary field. However, later fluoroscopic examination showed definite prominence of the cardiac shadow in the region of the pulmonary conus. These observations, in addition to the physical examination, led us to believe that the patient had a patent ductus arteriosus with bacterial vegetations at that site.

She was given a transfusion of 500 cc. of citrated blood. Because of the severity of her illness and because sulfanilamide had appeared to have a temporary beneficial effect on the patient in case 1 she was given the drug by mouth (fig. 2). Coincident with the administration of sulfanilamide there was a decline in the temperature, and the blood cultures remained sterile, with one exception.

The patient exhibited no untoward reactions to the drug. The hematuria, which was present for several days after admission, gradually subsided, with no reduction in renal function. Five weeks after entry, two additional transfusions were necessary because of a fall in the erythrocyte level. Three months after entry the value for hemoglobin was 82 per cent and the erythrocyte count 5,300,000 per cubic millimeter. The leukocyte count remained normal or slightly elevated throughout the course. An intradermal test made with a nucleoprotein fraction of hemolytic streptococcus gave a negative reaction on admission, but five weeks later, when the test was repeated, the result was strongly positive. There was

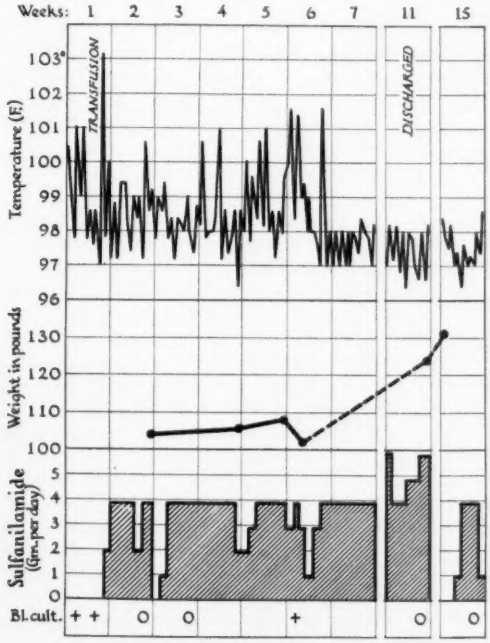

Chart. 2.—Subacute bacterial endocarditis due to Str. viridans. The patient became afebrile and gained weight, and the blood cultures remained sterile. The patient remained well nine months after sulfanilamide therapy.

gradual improvement in the patient's general condition. The liver and spleen were no longer palpable. The systolic and diastolic murmurs over the pulmonic area became more prominent, but no change was demonstrable in the size of the heart. The patient's weight two weeks after entry was 104 pounds (47.2 Kg.), and when she was discharged from the hospital, on December 14, her weight was 124 pounds (56.2 Kg.).

She was seen again nine months after leaving the hospital. She weighed 130 pounds (59 Kg.). Her only complaint was dyspnea on exertion. She was working daily in a truck garden. On examination the systolic and diastolic murmurs were found to be slightly more pronounced over the pulmonic area. The pulmonary

conus still showed enlargement when examined fluoroscopically. The spleen was palpable 2 fingerbreadths below the costal margin. She had not taken sulfanilamide during the intervening time.

The observations made in the preceding 2 cases lead one to assume an optimistic outlook concerning the value of sulfanilamide in the therapy of subacute bacterial endocarditis. We were fortunate in being able to study 10 additional patients and to observe less favorable results.

The following case is that of a patient with a congenital cardiac lesion, probably a patent interventricular septal defect with superimposed bacterial vegetations. Although she had a relatively mild clinical course, prolonged administration of sulfanilamide failed to sterilize the blood stream and did not appear to benefit her. Dr. Ruth Boynton, director of the University of Minnesota Health Service, and her associates gave us the opportunity of observing this patient.

CASE 3.—L. J., a 20 year old woman, single, entered the University of Minnesota Health Service on Feb. 14, 1938, complaining of weakness and fatigue. She had had dyspnea on exertion since early childhood. When she first entered grade school she was told that she had a cardiac murmur. On Jan. 6, 1938, she first noted lack of appetite and felt very tired. These symptoms were followed by headaches, generalized weakness and a slight fever. Rest in bed did not alleviate her symptoms, and she was advised to enter the hospital.

Physical examination showed her to be well developed and well nourished but apathetic and listless. Results of further examination were within normal limits except for a harsh systolic murmur at the apex. She presented a difficult problem in diagnosis. Pelvic and neurologic examination gave normal results. The spinal fluid showed no abnormality. The value for hemoglobin was 74 per cent. There were 4,470,000 erythrocytes and 12,900 leukocytes per cubic millimeter of blood. Culture of the blood on admission to the hospital showed no growth. The daily temperature ranged between 98.6 and 101.5 F. Approximately three weeks after admission she complained of pain at the base of the right great toe, and at this time small hemorrhagic areas appeared in the overlying skin on the plantar surface. Shortly thereafter the blood cultures contained Str. viridans, with 1 to 14 colonies per cubic centimeter of blood. A cutaneous test with the nucleoprotein of Streptococcus haemolyticus gave a negative result.

Since the illness appeared to be of short duration and the patient did not seem to be in serious condition, it was felt that sulfanilamide should be administered. She was given a total of 276 Gm. of the drug by mouth over a period of sixty-seven days. The daily dose varied between 60 and 75 grains. The cardiac murmur increased in intensity. There was no improvement in the clinical condition. There was continued evidence of bacteremia, although the cultures were occasionally sterile. The drug appeared to make the patient more lethargic and listless. In spite of anorexia she maintained her nutritional status. She had only moderate hypochromic anemia. No toxic manifestations were noted except for increased lethargy. It was apparent that sulfanilamide had been of no value to this patient, and she was sent home on May 17.

We had the opportunity in the following case of administering two different chemical compounds, to ascertain their effects. The patient was

first given sulfanilamide (paraaminobenzenesulfonamide) and then 4 (4′-aminobenzenesulfonamide) benzenesulfondimethylamide.

CASE 4.—N. N., a 25 year old white, single woman, entered the hospital on Sept. 10, 1937. She had been in good health up to four months previously, when she had a sore throat and severe occipital headaches. The sore throat persisted for three weeks and was accompanied by fever and progressive weakness. On three or four occasions she observed small red spots on her arms, which remained a few days and then disappeared. She had a cough productive of blood-streaked sputum and at one time had pain in the right lower part of the chest. She had never been known to have a cardiac lesion before her present illness. She had never had rheumatic fever or chorea.

On physical examination she appeared fairly well developed, but poorly nourished. There was marked pallor of the features and mucous membranes. The heart was found to be slightly enlarged on percussion. A systolic thrill was felt at the apex and another thrill just to the left of the sternum, in the third interspace. A loud, blowing systolic murmur was heard over the apex, which obscured the heart sounds and was transmitted to the axilla. A loud, rough systolic murmur was present in the third interspace, just to the left of the sternal border. The second pulmonic sound was accentuated. The rhythm was regular, and the blood pressure was 96 mm. of mercury systolic and 70 mm. diastolic. The lungs were within normal limits. The spleen and liver were not palpable. There was no edema of the lower parts of the legs.

The value for hemoglobin on entry was 57 per cent. There were 3,200,000 erythrocytes and 9,800 leukocytes per cubic millimeter of blood. Streptococci of the viridans type were cultured from the blood, and a pour plate showed 10 colonies per cubic centimeter of blood.

Fluoroscopic examination of the heart showed slight enlargement of the right and left ventricles, without any other demonstrable enlargement. There was no displacement posteriorly of the esophagus as observed after filling with barium sulfate.

A diagnosis of congenital heart disease with a patent interventricular septum was made. Because of her poor condition the patient was given three transfusions of bood during the first week of observation. This was followed by some improvement. During the third week she was given 45 to 60 grains (2.91 to 3.88 Gm.) of sulfanilamide a day. There was no appreciable change in her clinical condition during administration of the drug, although the blood cultures were sterile. She was then given 4(4′-aminobenzenesulfonamide) benzenesulfondimethylamide in smaller doses. Although her temperature approached normal, streptococci were isolated from the blood. She became extremely ill, with signs of congestive heart failure and jaundice. The medication was discontinued. She was given a transfusion of blood, but her condition became progressively worse, and she died on November 7. Autopsy was not performed.

The patient in the following case had marked bacteremia and an unusual type of cardiovascular lesion. After the oral administration of sulfanilamide the blood stream was sterilized and she became afebrile. Nevertheless, her illness terminated fatally. The case is reported in more detail elsewhere.[15]

15. Hallock, P., and Hebbel, R.: Coarctation of the Aorta, Nonclinical Type, Associated with Congenitally Bicuspid Aortic Valve: A Method for Its Recognition, Am. Heart J. **17**:444 (April) 1939.

CASE 5.—E. W., a 31 year old white woman, married, first entered the hospital on Aug. 14, 1937, complaining of pain in the left flank and intermittent chills and fever of about five months' duration. Physical examination showed that she was poorly developed and appeared chronically ill. There was a systolic pulsation in the suprasternal notch, with a systolic thrill. The heart did not appear enlarged on percussion. A soft midsystolic murmur was heard at the apex. Over the aortic area there was a low-pitched systolic murmur, followed first by an accentuated aortic second sound and then by a high-pitched, short diastolic murmur. The blood pressure was 104 mm. of mercury systolic and 70 mm. diastolic. Tenderness was elicited in the left flank on deep palpation, but no mass was felt. Fluoroscopic examination of the heart and great vessels by Dr. Philip Hallock showed dilatation of the aorta in the region of the common carotid and subclavian arteries, with a constriction between this dilatation and the ascending aorta.

It was thought that the patient had coarctation of the aorta and a congenital bicuspid aortic valve. She was febrile while under observation. On September 2 before further studies could be undertaken, she left the hospital, against advice.

She reentered the hospital on November 7. There had been no remarkable change in her condition until one week before, when she suffered from a sudden and sharp pain over the precordium, which radiated to the left shoulder and down the left arm. Such attacks, which were transient, occurred several times. She had had severe chills and a temperature of 104 F. At the time of admission she had petechiae of both conjunctivas and of the skin over the abdomen and chest. She complained of pain in the tips of her fingers. A harsh diastolic murmur was now heard over the aortic area and was transmitted down the left border of the sternum. The blood pressure was 130 mm. of mercury systolic and 60 mm. diastolic. The pressure was essentially the same in all four extremities. The margin of the liver was tender and was palpated 3 cm. below the right costal margin. The spleen was not felt.

The urine contained albumin, with leukocytes and erythrocytes in the sediment. The value for hemoglobin was 58 per cent. The erythrocyte count was 2,600,000 and the leukocyte count 6,000 per cubic millimeter. A blood culture on entry showed Str. viridans, with 100 colonies per cubic centimeter of blood.

The patient was given 90 grains (5.82 Gm.) of sulfanilamide a day for eleven days. The free sulfanilamide in the blood varied between 7 and 8.6 mg. per hundred cubic centimeters. Under this regimen the temperature approached normal and the blood cultures were sterile, but the patient's condition grew progressively worse. She died on November 27.

An autopsy, done by Dr. Robert Hebbel, disclosed a bicuspid aortic valve with soft, friable vegetations on the margins and scattered vegetations on the ventricular margins below the right cusp. Coarctation of the aorta was present. There were multiple infarcts of the kidneys and spleen.

Four patients were studied who had rheumatic heart disease with superimposed bacterial endocarditis. The patient in the following case was given small doses of sulfanilamide in order that the effect on the bacteremia and on the clinical course might be observed.

CASE 6.—A. S., a 23 year old white woman, married, entered the hospital on Nov. 4, 1937. Eleven years previously she had had acute rheumatic fever with resultant mitral valvulitis. Three years later she had congestive heart failure, followed by another attack of rheumatic fever. Four months before her present admission she noticed anorexia, weakness and dizziness. She became dyspneic

on exertion. Two months before admission she had chills and a temperature of 103 F. Profuse nocturnal sweats were present for two months. There was a recent loss of 25 pounds (11.3 Kg.) in weight.

On examination she appeared fatigued and chronically ill and showed evidence of recent loss of weight. There was marked pallor of the features and mucous membranes. Petechiae were present in the skin of the abdomen. The veins of the neck were distended. On percussion the heart was found to be enlarged, particularly in the region of the pulmonary conus. A systolic thrill was felt over the precordial area, with a loud, harsh systolic murmur on auscultation. No diastolic murmur was heard. The blood pressure was 110 mm. of mercury systolic and 70 mm. diastolic. The edge of the liver was felt 3 cm. below the costal margin, and the spleen was tender and easily palpable.

Laboratory data included the finding of erythrocytes and leukocytes in the sediment of the urine. The value for hemoglobin was 67 per cent; there were 3,500,000 erythrocytes and 19,400 leukocytes per cubic millimeter of blood. Cultures of the urine and blood yielded Str. viridans. There were 2 colonies per cubic centimeter of blood.

During her entire stay in the hospital the patient suffered from excruciating pain due to emboli. Her temperature ranged between 98.6 and 104 F. She perspired profusely. Sulfanilamide was given orally in doses of 40 grains (2.59 Gm.) daily for eleven days. The free sulfanilamide content of the blood varied between 3.3 and 4 mg. per hundred cubic centimeters. In addition, she was given two blood transfusions. Her condition became progressively worse. We wished to continue the administration of sulfanilamide in larger doses, but on December 18 she left the hospital against advice. She died at home three months later. Autopsy was not performed.

The patient in the following case had a severe form of rheumatic valvulitis involving the mitral and aortic valves. Coincident with the administration of sulfanilamide he became afebrile and felt greatly improved, but the blood cultures continued to show Str. viridans in large numbers.

Case 7.—R. S., a 36 year old white man, single, entered the hospital on Sept. 14, 1937. The patient had had his first attack of rheumatic fever nine years before entry, and since that time he had had recurrent attacks. He was known to have rheumatic involvement of both the aortic and the mitral valve. Five months before his present admission he had polyarthritis with chills and fever, which persisted until entry. He had progressive weakness, anorexia, nausea and vomiting.

On examination he appeared ill and poorly nourished. He had pallor and a suggestive icterus of the scleras. Petechiae were present in the conjunctivas. On percussion the heart was found to be enlarged to the left, with marked prominence of the conus. Systolic and diastolic murmurs were present over the apex. There was a diastolic murmur over the aortic area, which was transmitted down the left border of the sternum. The blood pressure was 124 mm. of mercury systolic and 50 mm. diastolic. The liver and spleen were not palpated.

The urine showed persistent albuminuria, with red blood cells, leukocytes and granular casts in the sediment. The value for hemoglobin was 56 per cent; there were 3,300,000 erythrocytes and 9,200 leukocytes per cubic millimeter of blood. A blood culture showed 65 colonies of Str. viridans per cubic centimeter.

The patient's temperature varied between 98.6 and 102 F. before the administration of sulfanilamide. He was given 60 grains (3.88 Gm.) of sulfanilamide daily for twenty-three days. Two blood transfusions were also given. After receiving the drug he became afebrile for nine days prior to leaving the hospital. He felt considerably improved. However, the organisms in cultures of the blood remained, quantitative studies showing 200 per cubic centimeter of blood. He was instructed to take the drug at home in doses of 60 grains (3.88 Gm.). After his discharge from the hospital, on October 14, his condition became worse, and he died at home three months later. Autopsy was not performed.

The patient in the following case had rheumatic heart disease with involvement of the mitral valve. Although the level of free sulfanilamide in the blood was 13 mg. per hundred cubic centimeters for several days, the bacteremia persisted, and the course terminated fatally.

CASE 8.—L. R., a 29 year old white woman, married, entered the hospital on July 13, 1938. She had scarlet fever at the age of 6 years, which was followed by "leakage of the heart." She had led a normal life and had four pregnancies, without any complications. Eight months before entry she had weakness, followed by many attacks of pleuritis. Five months later she had a persistent cough, severe anemia, swelling of the ankles and red spots on her arms and legs. Six weeks before entry she had hematuria, chills and fever.

On examination she appeared chronically ill. The mucous membranes were pale. Percussion showed that the heart was enlarged in the second and third left interspaces. A loud systolic murmur was heard over the entire precordium and was transmitted to the axilla and the back. There was no systolic murmur. The blood pressure was 168 mm. of mercury systolic and 65 mm. diastolic. Rales were heard at the bases of both lungs. The liver was palpable. The spleen was not felt.

Specimens of urine showed persistent albuminuria, with erythrocytes, leukocytes and cellular and granular casts in the sediment. The value for hemoglobin was 45 per cent; there were 3,800,000 erythrocytes and 15,000 leukocytes per cubic millimeter of blood. Cultures of the blood showed Str. viridans, with 360 colonies per cubic centimeter of blood.

The patient was given 60 grains (3.88 Gm.) of sulfanilamide orally each day for thirty-four days. She also received seventeen transfusions. The level of free sulfanilamide in the blood remained at 13 mg. per hundred cubic centimeters for several days. She continued to have bacteremia. Her temperature remained elevated. Her condition became progressively worse, and she died on August 27.

Autopsy.—The heart weighed 445 Gm. The leaflets of the mitral valve were destroyed by large fungating and ulcerating vegetations. A few vegetations were present on the aortic valve. There were infarcts of the spleen and left kidney. The kidneys showed acute proliferative glomerulonephritis.

The fourth patient with rheumatic heart disease and subacute bacterial endocarditis also received large amounts of sulfanilamide. The level of free sulfanilamide in the blood reached 18.3 mg. per hundred cubic centimeters, without any beneficial effect on the clinical course.

CASE 9.—W. B., a 66 year old white man, entered the hospital on July 21, 1938. Three months before entry he had a gastrointestinal disturbance and vomited

several times. After this he became weak and dyspneic and lost considerable weight. He had no chills or fever. There was no history of rheumatic fever, chorea or scarlet fever. His wife and one daughter had died of pulmonary tuberculosis.

The patient was emaciated and had rhythmic tremors of the arms and facial muscles. There were no petechiae of the skin or mucous membranes. On percussion the heart did not appear enlarged. There was a systolic murmur at the apex, which was transmitted to the axilla. The blood pressure was 112 mm. of mercury systolic and 62 mm. diastolic. The lungs were essentially normal. The spleen and liver were not palpable.

The urine persistently contained albumin, and leukocytes and erythrocytes were present in the sediment. The value for hemoglobin was 54 per cent; the erythrocyte count was 2,910,000 per cubic millimeter, and the leukocyte count was normal throughout the period of observation.

The diagnosis was doubtful until a culture of the blood showed Str. viridans, with 150 colonies per cubic centimeter. Roentgenologic examination of the patient's chest revealed enlargement of the left ventricle, with fulness in the region of the pulmonary conus.

The patient was given from 60 to 100 grains (3.88 to 6.48 Gm.) of sulfanilamide daily. In addition, he received five transfusions. The level of free sulfanilamide in the blood varied between 10 and 18.3 mg. per hundred cubic centimeters. The bacteremia persisted, and he continued to have a high fever. He showed no improvement. The cardiac murmur became louder; petechiae appeared in the mucous membrane of the eyes. He died on August 26.

Autopsy.—The heart weighed 375 Gm. There were large ulcerating lesions on the leaflets of the mitral valve. Smaller vegetations were seen on the leaflets of the aortic valve. The right lung had infarcts, and active tuberculosis was present in the apex of the left lung.

The following case is of considerable interest in that the patient was an elderly man with endocarditis involving the aortic valve. He had the signs and symptoms of subacute bacterial endocarditis. Sulfanilamide was administered, and severe anemia resulted. Although his blood became free of bacteria, there was no apparent change in the clinical course.

CASE 10.—J. M., a 70 year old white man, entered the hospital on Feb. 4, 1938. He had been examined two years previously in the hospital because of gastrointestinal symptoms. At that time no significant cardiac lesion was noted. Five months before his present admission he had dysuria, frequency, nocturia, anorexia and loss of weight. Three months later he had pain in the lower part of the back, fever, diarrhea and transient paralysis of the right side of the body.

Examination revealed the patient to be emaciated and dehydrated, with marked pallor. On percussion the heart appeared slightly enlarged to the left. The rhythm was regular. A systolic murmur was heard over the entire precordium. A faint diastolic murmur was heard over the third left interspace, close to the sternum. Marked peripheral arteriosclerosis was present. The blood pressure was 130 mm. of mercury systolic and 64 mm. diastolic. The edge of the liver was palpated 4 cm. below the costal margin. The spleen was not felt. The prostate was slightly enlarged.

The urine contained albumin, casts, red blood cells and leukocytes in the sediment. The value for hemoglobin was 65 per cent. The erythrocyte count was 3,100,000, and the leukocyte count, 12,700 per hundred cubic centimeters of blood. Cultures of the blood showed Str. viridans, with 200 colonies per cubic centimeter.

During the period of observation the patient's temperature ranged between 97 and 104 F. He was given 75 grains (4.88 Gm.) of sulfanilamide per day for one week; during this time cultures of the blood were sterile, but the temperature remained elevated and his general condition became worse. The diastolic murmur became more pronounced. The value for free sulfanilamide in the blood was 6 mg. per hundred cubic centimeters. At the end of one week of sulfanilamide therapy the value for hemoglobin was 36 per cent and the red blood cell count 1,950,000 per cubic millimeter. There was no icterus. The drug was discontinued. The patient's condition appeared hopeless. Arrangements for transfusions were undertaken, but his family took the patient home, against advice. He died one week later. Autopsy was not performed.

The last 2 patients included in this series had congenital heart disease with a patent ductus arteriosus. It is of interest to compare the results of sulfanilamide therapy in these cases with the results in case 2, as the same type of lesion was present. Sulfanilamide was administered to both patients over a long period without any appreciable beneficial effects.

Case 11.—L. M., a 40 year old white, single woman, entered the hospital on March 25, 1938. At 14 years of age she was told that she had "leakage of the heart." For years she had had dyspnea on exertion. Four months before entry she noticed progressive weakness. One month later a physician observed that she had fever and stated that she had pulmonary tuberculosis. Two months before entry she suffered from chills, fever and loss of weight. Another physician advised care at a sanatorium for tuberculosis. She entered a sanatorium, where she was observed for one month, but there was no evidence of pulmonary tuberculosis. She was then transferred to the University Hospitals.

Examination showed the patient to be poorly developed and poorly nourished. Petechiae were present in the mucous membranes of both eyes. Crepitant rales were heard over the lower lobe of the left lung posteriorly. The heart was found to be enlarged on percussion, particularly in the region of the pulmonary conus. A systolic thrill was felt over the region of the conus, and on auscultation a "machinery-like murmur" was heard. The pulmonic second sound was loud and snapping. The blood pressure was 130 mm. of mercury systolic and 68 mm. diastolic. The liver and spleen were not palpable. There was no peripheral edema.

Fluoroscopic examination of the heart and great vessels showed enlargement of the pulmonary artery and the right ventricle. A roentgenogram was interpreted as showing an infarct of the left lung.

The value for hemoglobin was 62 per cent. There were 3,400,000 erythrocytes and 22,000 leukocytes per cubic millimeter of blood. The initial blood culture contained Str. viridans, with over 100 colonies per cubic centimeter.

The patient was under observation in the hospital for eighty-three days. She was given a total of 4,140 grains (268.2 Gm.) of sulfanilamide in fifty-eight days. The average daily dose was about 70 grains (4.53 Gm.). The free sulfanilamide in the blood averaged 6.6 mg. per hundred cubic centimeters. The

highest level was 10.4 mg. per hundred cubic centimeters, observed while she was receiving 100 grains (6.48 Gm.) a day. Shortly after sulfanilamide was given, the blood cultures were sterile. When the drug was discontinued on two occasions for short periods, Str. viridans was isolated from the blood. The drug had no apparent effect on the temperature, as the patient was febrile throughout the period of observation. She was listless and had marked anorexia, which was apparently due to sulfanilamide. She lost 20 pounds (9.1 Kg.) in weight. It was apparent that the drug had only a temporary effect on the bacteremia; since she desired to go home, she left the hospital, unimproved, on June 15.

In the following case a patient with patent ductus arteriosus and bacterial vegetations was pregnant. The administration of sulfanilamide was deferred until a living child was born because of the possible toxic effects of the drug on the fetus.

CASE 12.—F. O., a 27 year old white woman, entered the hospital on May 21, 1938. She was known to have had a cardiac lesion since childhood, having had symptoms of dyspnea on exertion, fatigability and palpitation. About three months before entry she had an acute infection of the upper respiratory tract. Since that time she had complained of weakness, malaise and headache. She entered the hospital because of a threatened miscarriage. She was in the fifth month of pregnancy. There had been no previous pregnancies.

On examination she appeared chronically ill and poorly nourished. The mucous membranes of the eyes and mouth were pale, and no petechiae were observed. On percussion the heart was found to be enlarged in the region of the pulmonary conus. A continuous thrill was felt over the left second interspace. A typical "machinery-like murmur" was heard over this area, with both a systolic and a diastolic phase. The murmurs were transmitted to the left clavicle. The pulmonic second sound was accentuated. The lungs presented no abnormality. The blood pressure was 140 mm. of mercury systolic and 80 mm. diastolic. The fundus of the uterus reached the level of the umbilicus. The liver and spleen were not felt. There was no edema of the extremities.

Laboratory examination showed that the urine contained albumin, with erythrocytes and leukocytes in the sediment. The value for hemoglobin was 66 per cent; the erythrocyte count was 2,810,000 and the leukocyte count 18,900 per cubic millimeter of blood. Str. viridans was isolated from the blood on many occasions, with 1 to 181 colonies per cubic centimeter.

Roentgenologic examination of the heart showed definite enlargement of the pulmonary conus and of the right ventricle. Prior to delivery the patient was given several transfusions. She had frequent chills and was febrile. She suffered from severe pulmonary infarcts. Approximately two and one-half months after entry she had spontaneous labor, and a living child was born. Shortly after delivery, a culture of the patient's blood showed Str. viridans; the cord blood of the infant was sterile. After several transfusions the patient improved slightly, but she continued to have pulmonary infarcts. About one week post partum she was given sulfanilamide by mouth. The doses varied between 45 and 60 grains (2.91 and 3.88 Gm.) a day. The free sulfanilamide in the blood averaged 3 mg. per hundred cubic centimeters. She tolerated the drug poorly, suffering from anorexia and vomiting. She remained febrile. The bacteremia persisted. Under the circumstances, sulfanilamide therapy was discontinued, and she was sent home on September 1.

COMMENT

The primary purpose in the study of these cases was to evaluate the effect of sulfanilamide on the clinical course of subacute bacterial endocarditis. Although the number of cases is small, it appears that the drug had a definite beneficial effect on 2 of the 12 patients. In case 1 there was evidence of meningitis in addition to bacterial endocarditis. The clinical and anatomic evidence indicates that there was no residue of the acute attack of meningitis. We are not aware of any reports in the literature of cases in which sulfanilamide has been of any value in the treatment of meningitis due to Staph. albus. Block and Pacella [16] reported a case of staphylococcic meningitis in a child 17 days old, in which a cure was apparently obtained with sulfanilamide. No statement was made as to whether the organism isolated was Staph. albus or Staphylococcus aureus. By permission of Dr. Irvine McQuarrie and his associates, of the department of pediatrics at the University Hospitals, we had the opportunity of observing a 3 year old child who had meningitis due to Staph. albus. Sulfanilamide was given to this patient for a long period, but the disease terminated fatally. Another child, 17 months old, had meningitis due to Staph. aureus. He also had hydrocephalus. Administration of sulfanilamide was followed by recovery from the meningitis.

After the diagnosis of bacterial endocarditis had been established in case 1, the patient was apparently "cured" and remained so for seven months. Of considerable interest were the minimal changes observed in the endocardium at autopsy. Bacterial endocarditis was apparently engrafted on a previously normal valve. The lack of extensive damage to the mitral valve over such a long period might be explained on the basis of invasion of tissues by an organism of low virulence or by the bacteriostatic effect of sulfanilamide. It is interesting to speculate on the outcome of this patient's illness if sulfanilamide had been prescribed for a long period after her first discharge from the hospital.

At the time of writing, the second patient in this series has been in good health for nine months after sulfanilamide therapy. Whether there is only a remission in her disease or whether she is cured will be answered only by a prolonged period of observation. It is important that before sulfanilamide was given a quantitative study of blood cultures showed 30 colonies of Str. viridans per cubic centimeter of blood on one occasion and 200 colonies on another. In the remaining 10 cases we do not believe that sulfanilamide therapy had any desirable effect on the course of the disease.

16. Block, H., and Pacella, B. L.: Staphylococcic Meningitis: Report of a Case in a Seventeen Day Old Infant Successfully Treated with Sulfanilamide. J. A. M. A. **110**:508 (Feb. 12) 1938.

There is little doubt that in some patients the administration of sulfanilamide will render the blood stream sterile, as determined by cultures of venous blood. This was true of 6 of the 12 patients in this series. However, this bactericidal effect appeared to be only temporary, except in cases 1 and 2. We observed 2 patients in whom the blood was rendered free of bacteria by sulfanilamide, but when administration of the drug was discontinued for forty-eight hours bacteremia was again established. In 6 patients the prolonged administration of sulfanilamide did not sterilize the blood. It is likely that the organisms in the vegetations are protected from the action of sulfanilamide, even though the drug may have a bactericidal effect on those that reach the blood stream. It may be that certain strains of Str. viridans are more readily destroyed by sulfanilamide than others. We have initiated a study of this problem.

All of the 12 patients were febrile during their illnesses. In 4 there was a definite decline of the temperature, coincident with the administration of sulfanilamide. The temperature became normal or was only slightly elevated. In 5 patients the drug did not appear to affect either the temperature or the bacteremia. The patient in case 3 had only a low grade fever throughout the period of observation, and there were only 1 to 14 colonies of organisms per cubic centimeter of blood. Yet sulfanilamide therapy had no effect on either the fever or the bacteremia. The patient in case 6 had a high fever and persistent bacteremia, neither of which was affected by sulfanilamide. In 1 patient (case 7) after sulfanilamide was given the temperature became and remained normal but the bacteremia was unaffected. In 2 patients (cases 10 and 11) sulfanilamide therapy was accompanied by sterilization of the blood, but was without effect on the temperature. We did not observe any instance of "drug fever," as described by Hageman and Blake.[17]

Although all the patients had some degree of anemia during their illness, in only 1 could a rapid decline in the hemoglobin and erythrocyte levels be attributed to sulfanilamide. In case 10 5 Gm. of the drug was given daily for one week. During this time the value for hemoglobin dropped from 51 to 36 per cent, and the erythrocyte count, from 2,500,000 to 1,950,000 per cubic millimeter. There was no further decline when the drug was discontinued. In no instance did sulfanilamide cause a depression of the leukocyte level. In 2 patients (cases 4 and 11) there was a definite and marked increase of the leukocytes during the administration of sulfanilamide.

17. Hageman, P. O., and Blake, F.: A Specific Febrile Reaction to Sulfanilamide, J. A. M. A. **109**:642 (Aug. 28) 1937.

Sulfanilamide Therapy in 12 Cases of Bacterial Endocarditis

Case, Sex and Age in Years	Duration of Symptoms Before Treatment, Wk.	Cardiac Lesion		Causative Organism with Number of Colonies per Cc. of Blood	Sulfanilamide Therapy			Time Under Observation	Comment
		Cause	Anatomic Type		Total Dose, Gm.	Toxic Signs and Symptoms	Result		
1 F 35	28	Bacteria implanted on normal valve	Mitral stenosis	Staph. albus; 4 to 11	135 in 45 days; 124.5 in 56 days	None on first admission; nausea, vomiting, anorexia, loss of weight on second admission	Spinal fluid sterilized; blood sterilized; temperature normal; Staph. albus on heart valve at autopsy	11 months	Afebrile 203 days; gained 40 pounds in weight; had ? remission or reinfection; died; autopsy
2 F 18	8	Congenital	Patent ductus arteriosus	Str. viridans; 30 to 200	191.6 in 58 days	None; transfusion before sulfanilamide	Blood sterilized; temperature normal	11 months	Good health 9 mo. after leaving hospital; cure (?)
3 F 20	5	Congenital	Patent interventricular septum	Str. viridans; 1 to 14	276 in 67 days	Listlessness, lethargy, anorexia	No effect on bacteremia or temperature	92 days	Discharged home; no improvement
4 F 25	16	Congenital	Patent interventricular septum	Str. viridans; 10	53.2 in 23 days	Nothing definite; signs of failure of right heart with jaundice and cyanosis	Blood sterilized while drug given; bacteremia when omitted; temperature normal	59 days	Died 59 days after first seen; no autopsy
5 F 31	20	Congenital	Coarctation of aorta; bicuspid aortic valve	Str. viridans; 100	64 in 11 days	Difficult to evaluate; listlessness, weakness, anorexia	Blood cultures sterile; temperature approached normal; Str. viridans on heart valve at autopsy	28 days	Died; autopsy
6 F 23	8	Rheumatic	Mitral stenosis	Str. viridans; 200	42.6 in 11 days	Nothing definite because of toxicity from disease	No effect on bacteremia or temperature	34 days	Left hospital against advice; died 3 mo. later; no autopsy
7 M 36	12	Rheumatic	Mitral stenosis; aortic regurgitation	Str. viridans; 65	87.7 in 23 days	None	No effect on bacteremia; normal temperature	30 days	Died 3 mo. after leaving hospital; took drug at home; no autopsy
8 F 29	12	Rheumatic	Mitral stenosis	Str. viridans; 360	131.6 in 34 days	Anorexia, anemia; repeated transfusions necessary	No effect on bacteremia or temperature	51 days	Died; autopsy
9 M 66	10	Rheumatic	Mitral stenosis	Str. viridans; 150	102.5 in 19 days	Nothing definite; toxic before sulfanilamide therapy	No effect on bacteremia or temperature	36 days	Died; autopsy
10 M 70	8-20	? Arteriosclerotic	Aortic regurgitation	Str. viridans; 200	33.87 in 7 days	Severe anemia for 1 week	Blood sterilized; no effect on temperature	22 days	Died 1 wk. after leaving hospital, against advice; no autopsy
11 F 40	12	Congenital	Patent ductus arteriosus	Str. viridans; 100	267 in 58 days	Listlessness; lethargy; anorexia	Blood sterilized; bacteremia when drug omitted; no effect on temperature	83 days	Discharged home; no improvement
12 F 27	12	Congenital	Patent ductus arteriosus	Str. viridans; 1 to 181	95.8 in 36 days	Anorexia; vomiting	No effect on bacteremia or temperature	119 days	Pregnant; delivered of living premature baby; sulfanilamide after delivery; discharged home; no improvement

The level of free sulfanilamide in the blood of these patients was determined at frequent intervals. We could find no definite relation between the amount present in the blood and its effect on the bacteremia. The highest level was 18.3 mg. per hundred cubic centimeters (case 9). In the patient who was apparently cured (case 2) the sulfanilamide level varied between 5.3 and 8.5 mg. per hundred cubic centimeters. In 1 patient the blood cultures remained sterile when the sulfanilamide level of 3.1 mg. per hundred cubic centimeters was reached. Tests in vitro showed that sulfanilamide had a marked bacteriostatic effect on the organisms in this case. Another patient continued to have bacteremia with a level of 10.6 mg. of sulfanilamide per hundred cubic centimeters of blood.

Difficulty was experienced in evaluating the toxic effects of the drug because the disease itself complicated the symptoms. A majority of the patients had anorexia during the administration of sulfanilamide. This was so severe in some of the patients that the drug had to be discontinued. The patients also appeared listless and lethargic in varying degrees while taking the drug. It is of considerable interest that none of the patients exhibited more than a slight degree of cyanosis. The carbon dioxide–combining power of the patients' blood was observed at frequent intervals, and no patient had acidosis. One patient (case 1) had nausea and vomiting due to the drug after she had taken it for several weeks. Anorexia and vomiting were prominent features in the illness in case 2, and sulfanilamide had to be discontinued because of these symptoms.

SUMMARY

Sulfanilamide was administered to 12 patients with subacute bacterial endocarditis. The etiologic agent was Str. viridans in 11 patients and Staph. albus in 1. Of the 2 patients who appeared definitely improved after receiving the drug, 1 eventually died of the disease, and at the time of writing the other has been well for nine months.

All the patients had bacteremia. Sulfanilamide rendered the blood stream sterile in 6 of the 12 patients. This bactericidal effect appeared to be only temporary, except in 2 patients.

In 4 patients there was a decline in the temperature coincident with the administration of sulfanilamide. There did not appear to be any relation between the degree of fever and the therapeutic effect of sulfanilamide.

Although the drug was taken for a long period by several of the patients, there was a marked decline in the erythrocyte level in only 1 case. In none was a depression of the leukocytes observed.

There was no definite relation between the amount of free sulfanilamide in the blood and the effect of the drug on the bacteremia.

The use of sulfanilamide in the treatment of patients with subacute bacterial endocarditis is of doubtful value because of the nature of the focus of infection.

CONCLUSION

It appears from the foregoing observations that the administration of sulfanilamide to patients with subacute bacterial endocarditis will in some instances render the circulating blood free of organisms. Except for 2 of the patients, this bactericidal effect was only temporary and depended on the continued use of the drug. In 2 patients definite improvement followed the use of sulfanilamide. However, we believe that sulfanilamide and its related compounds will be of doubtful value in the treatment of patients with subacute bacterial endocarditis because of the very nature of the focus of infection. The proliferating mass of bacteria situated well beneath the surface of the vegetation is probably protected, at least in part, from the action of free sulfanilamide in the blood, as well as of specific antibodies. When the organisms approach the surface of the vegetation, they are carried off in the circulating blood, and under these circumstances may be killed. An analogous therapeutic situation is now recognized in the treatment of patients with bacteremia due to beta hemolytic streptococci. Lockwood [18] stated that in a number of instances of infection of the blood stream an infected thrombus in a large vessel has prevented satisfactory elimination of the bacteremia.

Since the presence of sulfanilamide in the blood may have a bacteriostatic effect on some strains of Str. viridans, sulfanilamide probably should be administered to any patient with valvular lesions who may be subjected to oral surgical procedures. It is well known that after the extraction of teeth or after a tonsillectomy temporary bacteremia with Str. viridans may result.

18. Lockwood, J. S.: Observations on the Mode of Action of Sulfanilamide and Its Application to Surgical Infections, Ann. Surg. **108**:801 (Nov.) 1938.

MYOCARDIAL INFARCTION WITHOUT SIGNIFICANT LESIONS OF CORONARY ARTERIES

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NEW YORK

Since Heberden's [1] famous description of the clinical syndrome of angina pectoris and the subsequent finding of associated calcification of the coronary arteries by Jenner [2] and his pupil Parry,[3] the controversy about the etiologic role of narrowing of the coronary arteries in Heberden's syndrome has never ceased to hold interest. Until recently all objections have been based on the frequent disparity between the anatomic and the clinical features. The difficulty in correlating morbid anatomy, on the one hand, with disturbed physiology, on the other, has been epitomized by Aschoff.[4] Similar discrepancies between the location and size of the myocardial infarction and the corresponding vascular lesion have been indicated.

The occurrence of major myocardial damage with a minimum or even absence of coronary disease is not rare. S. A. Levine [5] cited 11 of his own cases studied at autopsy in which major myocardial lesions were accompanied by corresponding disease of the coronary arteries. In a study of 100 cases of myocardial infarction Lisa and Ring [6] found 8 in which the lesions in the vessels were minimal or the vessels were normal. Barnes and Ball,[7] Brown,[8] Davenport [9] and others observed

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1. Heberden, W.: Some Account of a Disorder of the Breast, Med. Tr. Roy. Coll. Phys. London **2**:59, 1786.

2. Jenner, E., cited by Parry.[3]

3. Parry, C. H.: An Inquiry into the Symptoms and Causes of the Syncope Anginosa, Commonly Called Angina Pectoris, London, Cadell & Davis, 1799.

4. Aschoff, L., and Tawara, S.: Die heutige Lehre von der pathologisch-anatomischen Grundlagen der Herzschwäche, Jena, Gustav Fischer, 1906.

5. Levine, S. A.: Coronary Thrombosis, Baltimore, Williams & Wilkins Company, 1929.

6. Lisa, J. R., and Ring, A.: Myocardial Infarction or Gross Fibrosis: An Analysis of One Hundred Necropsies, Arch. Int. Med. **50**:131 (July) 1932.

7. Barnes, A. R., and Ball, R. G.: The Incidence and Situation of Myocardial Infarction in One Thousand Consecutive Postmortem Examinations, Am. J. M. Sc. **183**:215, 1932.

(Footnotes continued on next page)

instances of myocardial infarction without complete coronary occlusion. Krumbhaar and Crowell [10] reported cases of arteriosclerotic heart disease associated with rupture of the myocardium in areas where the coronary arteries were patent. Several interesting cases are recorded by Jaffé and Bross.[11] These were instances of sudden death due to rupture of the left ventricle in which the coronary vessels were normal, but microscopically there were numerous areas of focal necrosis. They concluded that the lesions were due to an acute circulatory disturbance. V. Levine [12] studied cases of diffuse myocardial fibrosis with patency of the coronary arteries, but in these cases frank infarction was not present.

Our study adds 15 new instances of extensive myocardial infarction in which the intimal changes in the coronary arteries were insignificant and the lumens not materially narrowed. It is our intention in this paper to consider the functional factors which could produce circulatory disturbances severe enough to cause necrosis of the cardiac muscle even though the lumens of the coronary arteries remained patent.

There were 8 men and 7 women, the ages ranging from 41 to 78. Five of the patients had an anginal syndrome, 5 others had a history of dyspnea on exertion without anginal pain, 1 had rheumatic heart disease and 4 had no symptoms referable to the heart.

Hypertension was frequent. Blood pressure readings of 150 systolic and 90 diastolic were accepted as the upper limits of normal. A definite history of hypertension was obtained in 9 of the 15 cases. In 4 others, hypertension was probable in view of the marked cardiac hypertrophy not explained by other causes. In 1 case the blood pressure was elevated, though the heart weighed 340 Gm. It is obvious from either the elevated blood pressure or the increased heart weight that the majority of our cases, 13 of 15, were most likely instances of present or antecedent hypertension. The very fact that this type of myocardial damage with a small or no vascular lesion occurs so frequently with hypertension is itself of striking interest.

Cardiac hypertrophy was deemed to have existed when the heart weighed 350 Gm. or more or when microscopic slides showed generalized fibrous hypertrophy in a heart weighing less. While this figure is in some measure arbitrary, it is generally accepted as the upper limit of normal. In 12 cases the heart weighed 350 Gm. or more.

8. Brown, M. R.: A Study of the Pathogenesis of Myocardial Fibrosis ("Chronic Fibrous Myocarditis"), Am. J. M. Sc. **184**:707, 1932.

9. Davenport, A. B.: Spontaneous Heart Rupture—A Statistical Summary, Am. J. M. Sc. **176**:62, 1928.

10. Krumbhaar, E. B., and Crowell, C.: Spontaneous Rupture of the Heart, Am. J. M. Sc. **170**:828, 1925.

11. Jaffé, R., and Bross, K.: Histologische Befunde bei Herzrupturen, Centralbl. f. allg. Path. u. path. Anat. **56**:246, 1933.

12. Levine, V.: Myocardial Changes in Hypertension, Arch. Path. **18**:331 (Sept.) 1934.

Congestive heart failure was present in 7 cases and varied in duration from three months to seven years. The average weight of the heart in cases of chronic congestive heart failure was 587 Gm. The

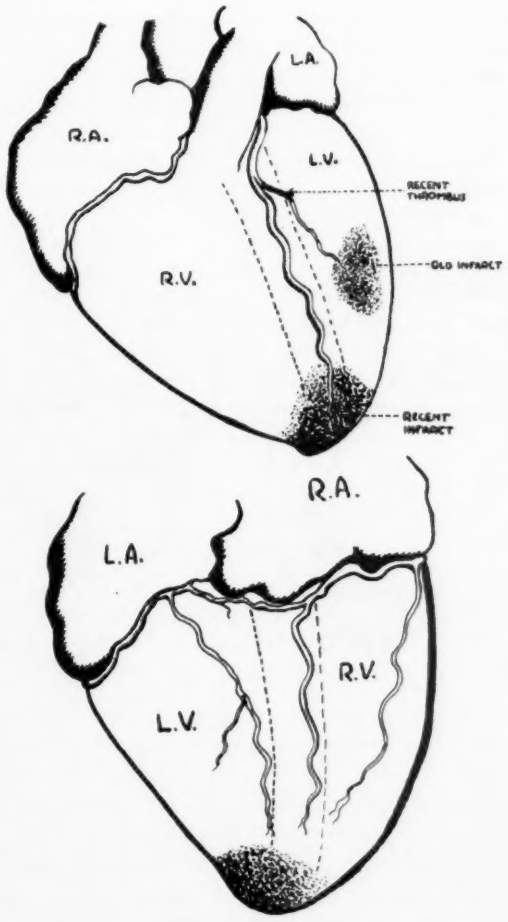

Fig. 1 (case 13).—Anterior and posterior view of the heart, which weighed 810 Gm.

average weight in cases in which there was no congestive heart failure was 367 Gm. Myocardial damage was common to both groups; only patients with failure had great cardiac enlargement.

CORONARY ARTERIES

In our 15 cases the vessels, in general, showed only a slight degree of arteriosclerosis, with good-sized lumens in all. The condition of the coronary arteries was comparable to that of a normal group of persons of similar ages. The need for thorough anatomic dissections in such cases is apparent. If the vessels are opened lengthwise, it is conceivable that a small thrombus may be dislodged and pushed aside. If the vessels are transected, a small occlusion may be overlooked unless the sections are made at minute intervals. In our series the blood vessels were sectioned transversely and checked by microscopic sections of different portions of the heart. In 4 of the hearts, we made extremely minute

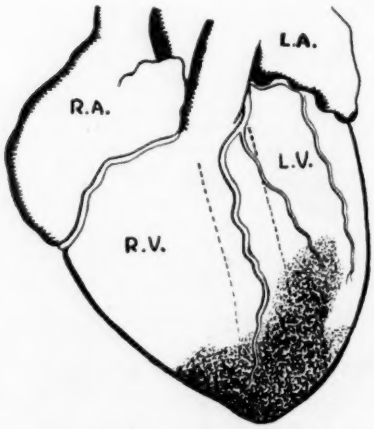

Figure 2

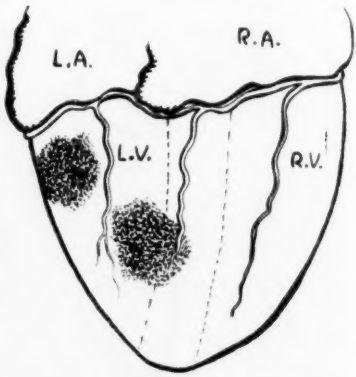

Figure 3

Fig. 2 (case 14).—Anterior view of the heart, which weighed 480 Gm.
Fig. 3 (case 15).—Posterior view of the heart, which weighed 290 Gm.

dissections of the coronary arteries before and after fixation. In 1 case serial sections of the entire major arterial tree were cut. In all our cases vascular involvement was slight. In no instance was there appreciable narrowing of the coronary arteries.

In some hearts occasional small intimal plaques were encountered. Microscopically these showed the usual changes, with fibrosis and lipoid-laden mononuclear cells. Occasional minute areas of calcification were found. The lumens, however, were nowhere significantly reduced, and there was no evidence of recanalization, intimal hemorrhage or arteritis at any point. The case in which serial sections were made is particularly pertinent. The vessels throughout their course were elastic and collapsed, and arteriosclerosis was minimal.

MYOCARDIAL INVOLVEMENT

Of the 15 patients, 1 showed acute myocardial infarction, while the 14 others showed healed myocardial infarction. The localization of myocardial lesions in this group followed, in general, the same areas of predilection observed in patients with coronary sclerosis and thrombosis. The left ventricle was most frequently involved, namely, in 14; and the right ventricle was involved in 1. The area usually supplied by the anterior descending ramus of the left coronary artery was the most frequent site.

The sites of infarction and fibrosis were as follows:

	No. of Cases		No. of Cases
Infarction of posterior wall	1	Interventricular septum and papillary muscle	1
Infarction of posterior wall; fibrosis of left ventricle	1	Interventricular septum and apex of left ventricle	1
Infarction at apex	3	Septum and anterior and posterior walls of right ventricle	1
Infarction at apex; diffuse fibrosis	1	Septum, apex, anterior (old) and posterior (recent) walls	1
Infarction at apex; diffuse fibrosis with aneurysmal dilatation	1	Apex, left ventricle and septum	1
Posterior wall of right ventricle	1	Anterior and posterior walls and septum	1
Interventricular septum	1		

The coronary arteries were essentially normal.

VALVULAR INVOLVEMENT

One patient had arteriosclerotic aortic insufficiency and stenosis. Another had mitral stenosis and insufficiency and aortic insufficiency of rheumatic origin. A patient not reported on in this study had rheumatic aortic insufficiency with myocardial infarction of the posterior wall of the left ventricle.

COMMENT

The basic physiologic factor in angina pectoris and coronary disease, as has been maintained by Rothschild and Kissin,[13] Keefer and Resnik[14] and others, is a state of imbalance between the myocardial need of oxygen and the supply of oxygen. This imbalance, depending on its severity and its duration, may lead to different phenomena, varying from transitory anginal pain to extreme myocardial damage. In its severest form it may lead to sudden death with or without myocardial infarction.

13. Rothschild, M. A., and Kissin, M.: Anginal Syndrome Induced by Gradual General Anoxemia, Proc. Soc. Exper. Biol. & Med. **29**:577, 1932.

14. Keefer, C. S., and Resnik, W. H.: Angina Pectoris: A Syndrome Caused by Anoxemia of the Myocardium, Arch. Int. Med. **41**:769 (June) 1928.

Clinical and Pathologic Data in Fifteen Cases of Myocardial Infarction Without Significant Lesions in the Coronary Arteries

Case, Sex, Age	Cardiac Weight, Gm.	Blood Pressure	Symptoms and Signs	Pathologic Data
1 M 70	340	185-190/85	Diabetes mellitus, 20 yr.; amputation of right leg 2 yr. before admission; gangrene of left foot, 2 mo.; no anginal pain; no congestive heart failure; sudden death probably due to cardiac failure	Superficial atheromas of coronary arteries with slight calcification; lumens of good size throughout; healed infarct of posterior wall of left ventricle; diffuse fibrosis of left ventricle; arteriosclerotic gangrene of left leg; thrombosis of iliac arteries
2 F 63	380	145/80	Headaches, 1 yr.; right hemiplegia, 1 mo.; hepatomegaly and splenomegaly; no history of anginal pain or congestive failure; polycythaemia vera; death from bronchopneumonia	Moderate coronary atherosclerosis; lumens of good size throughout; healed infarct of apex of left ventricle; splenomegaly; thrombosis of adrenal and pituitary veins
3 F 48	270	100/65	Carcinoma of cervix with metastasis to lumbar portion of spine and brain; tachycardia, extrasystoles; no anginal pain or congestive heart failure; died in uremia	Occasional intimal plaques in coronary arteries; 2 healed infarcts at middle of posterior wall of left ventricle, largest measuring 1.5 by 1.5 by 5 cm.; papillary cystadenoma of ovary with metastasis; arteriosclerosis of kidneys; uremia
4 F 41	350	150/80	Collapsed in anginal seizure; shortly thereafter dyspnea and edema of legs; advanced congestive failure, 3 mo.; death due to bronchopneumonia	Slight coronary atherosclerosis; lumens of good size throughout; infarct of apex of left ventricle with mural thrombosis; cardiac hypertrophy and dilatation; thrombi in both auricles; chronic passive congestion of viscera; ascites; healed infarcts of spleen and kidney
5 M 52	350	140-156/90-110	Right hemiplegia, 8 yr.; pain in left hypochondrium; heaviness and discomfort, 3 yr.; dyspnea on exertion, 4 yr.; polycythaemia vera; hepatic and splenic enlargement; not in congestive heart failure; electrocardiogram showed prominent Q_1 and Q_2; T_1 inverted; T_2 flat; T_3, low voltage; death from cerebral insult	Few small atheromatous areas in coronary arteries with no encroachment on lumens; healed infarct of apex of left ventricle with aneurysmal dilatation and mural thrombus; diffuse fibrosis of both ventricles; chronic passive congestion of viscera; splenomegaly; healed and recent splenic infarcts; massive infarction of adrenals; duodenal ulcer; arteriolosclerosis of kidneys
6 M 54	750	170/120	Headaches, 20 yr.; dyspnea on exertion and cardiac asthma, 4 yr.; no anginal pain; advanced congestive heart failure, 7 yr.; death from cerebral insult	Small plaques scattered in coronary arteries; lumens widely patent throughout; healed infarct of apex of left ventricle, 1.5 cm. in diameter; small patches of fibrosis elsewhere; hydrothorax; hydropericardium; healed and recent infarcts of spleen; arteriolosclerosis of kidneys
7 F 44	520	154-160/90	Rheumatic fever at 14 and again 6 mo. before admission; mitral stenosis and mitral insufficiency; auricular fibrillation; left hemiplegia; advanced congestive heart failure, 4 yr.; anginal pain, 2 mo.; electrocardiogram showed small Q_1; inverted T_2 and T_3; sudden death	A few small plaques in coronary arteries; lumens widely patent everywhere; healed infarcts at upper portion of posterior wall of left ventricle, 3.5 cm. in diameter, and at lower portion of intraventricular septum and anterior two thirds of left ventricle; old and recent rheumatic endocarditis of mitral and aortic valves; mural thrombi of auricular appendage; healed infarcts of spleen and kidneys; cerebral embolism
8 F 77	500	145/80	Weakness, dyspnea and edema of extremities, 5 yr.; no history of angina pectoris; death from progressive congestive heart failure	A few atherosclerotic plaques in coronary arteries; lumens of good size throughout; healed infarct of apex of left ventricle, 4 by 3 cm.; atherosclerotic aortic insufficiency and stenosis; bilateral hydrothorax; generalized arteriosclerosis
9 M 78	800	136/70 Hypertension known, 2 yr.	Left hemiplegia, 2 yr. before admission; several anginal attacks in 2 mo.; death from progressive congestive failure	Moderate sclerosis at mouths of coronary arteries; a few small plaques in widely patent vessels; healed infarct of apex of left ventricle involving interventricular septum; emphysema; generalized arteriosclerosis

Clinical and Pathologic Data in Fifteen Cases of Myocardial Infarction Without Significant Lesions in the Coronary Arteries—Continued

Case, Sex, Age	Cardiac Weight, Gm.	Blood Pressure	Symptoms and Signs	Pathologic Data
10 M 49	600	150-220/110-130	Dyspnea and cough, 7 yr.; congestive failure, 5½ yr.; auricular fibrillation; no anginal pain; electrocardiogram showed inverted T_1; flat T_2; high RT_3 transition; slurring of QRS; PR interval, 0.24 sec.; sudden death	A few atheromatous plaques in larger branches of coronary arteries; lumens patent throughout; healed infarct of posterior wall of right ventricle, 1.5 cm. from apex, measuring 4 by 4.5 cm.; ascites; bilateral hydrothorax; generalized arteriosclerosis and renal arteriolosclerosis
11 F 59	470	132/90	Dyspnea, 6 mo.; senile psychosis; no anginal pain or congestive failure; electrocardiogram showed inverted T_1; high take-off of T_2 and T_3; slurring of all QRS complexes; intraventricular conduction disturbance; auricular fibrillation; sudden death	Coronary arteries thinly atheromatous and patent throughout; healed infarct of interventricular septum and apex of left and right ventricles; pulmonary infarcts; renal arteriosclerosis and arteriolosclerosis; diffuse arteriosclerosis; bilateral fibroid tuberculosis with cavitation
12 M 62	350	115/70	Pain and burning in left leg, 6 yr.; severe pain in right side of chest and back, 6 mo.; no congestive failure; electrocardiogram showed auricular fibrillation; low take-off of T_1 and T_2, which were inverted; death from gangrene of left leg	Very slight atherosclerosis of coronary arteries which were patent throughout; healed infarct of interventricular septum near apex, 1.5 cm.; bilateral pulmonary tuberculosis with cavitation; thrombosis of left common iliac artery; gangrene of left leg
13 M 75	810	160/105	Edema of ankles, 5 yr.; no history of angina pectoris; congestive heart failure, 5 yr.; exact cause of death not known; had infection of arm, recent occlusion of small coronary artery and ulcers of duodenum	Moderate sclerosis of first 3 cm. of left anterior descending coronary artery; lumen of good size throughout; small branch of left anterior descending artery given off 3 cm. from origin, extended diagonally along left ventricle and was occluded by a recent thrombus; right coronary artery showed slight atherosclerosis with lumen of good size throughout; recent infarction of apex, anterior and posterior wall of left ventricle and septum, 5 by 4 cm.; mural thrombus; old infarct of anterior wall of left ventricle, 5 by 6 cm.; recent occlusion near old infarct; recent infarct not related to recent occlusion, which was very small; infarct of spleen; arteriolosclerotic aneurysm of splenic artery; arteriolosclerosis of kidneys; multiple subacute ulcers of duodenum; cerebral arteriosclerosis (fig. 1)
14 F 57	480	136/110	Angina pectoris, 2 or 3 yr.; anorexia, nausea, vomiting and dyspnea on exertion, 7 mo.; no congestive failure; Grawitz tumor of left kidney with metastasis; sudden death	Slight thickening of walls of first portion of major branches of coronary arteries; walls elastic and lumens widely patent throughout; areas of thinned-out myocardium in anterior and posterior walls of left ventricle; old large infarct of septum except for upper 5 cm. extending to anterior and posterior walls of left ventricle and portion of right ventricle near septum; hypertrophy and dilatation of heart; Grawitz tumor of left kidney; fibromas of uterus, left ovary and stomach (fig. 2)
15 M 62	290	.....	Weakness, anorexia and cough for 1 yr.; severe anemia; no history of angina pectoris or congestive failure	Coronary arteries thin walled and elastic; lumens widely patent; left circumflex branch on posterior wall of narrow caliber but thin and elastic wall; no occlusion; 2 old infarcts on posterior surface of left ventricle including posterior papillary muscle; hypernephroma of right kidney with metastasis to left kidney, adrenals, lungs, brain and epicardium (fig. 3)

The physiologic mechanisms whereby this delicate balance of oxygen need and supply is maintained are widespread and complex. The heart is a continuously functioning organ. Further, it is unique in that its nourishment depends on the coronary flow which it must itself supply. Its crucial situation is expressed by the wide variety of physiologic phenomena, both cardiac and extracardiac, which, with few exceptions, are directed toward increasing its blood supply rather than to yielding blood for purposes elsewhere. Its nourishment and proper function depend on reflex and humoral factors involving many organs, including the proper surrendering of blood by the depot organs, the liver, spleen and skin.

Failure of any of these compensatory mechanisms may initiate myocardial anoxia. Such failure may account not only for the cases of extreme infarction with minimal coronary disease, such as we have reported, but for the frequently observed discrepancy between the degree of vascular disease and the condition of the myocardium. It is worth while therefore to review these physiologic mechanisms, failure of which may produce myocardial ischemia in the absence of obvious vascular occlusion.

Factors Affecting Myocardial Nutrition

I. Mechanical Factors
  1. Fall in aortic blood pressure, especially in peripheral shock
  2. Phasic variations in coronary flow:
     Aortic insufficiency; arteriovenous fistula
     Aortic stenosis
     Hypertension
  3. Cardiac hypertrophy
  4. Tachycardia
  5. Failure of adequate collateral circulation; anomalies of coronary arteries

II. Changes in Blood
  1. Anemia
  2. Polycythemia

III. Reflex Factors
  (*A*) Coronary Vasomotor Reflexes
     Anoxemia due to
       (*a*) Failure of compensatory dilatation due to
         1. Inadequate reflex response
         2. Sclerosis of vascular walls
       (*b*) Marked vasoconstriction

  These reflexes may be classified as
  1. Reflexes originating in heart and associated structures
       (*a*) Proprioceptive reflexes adapting coronary flow to increased work, etc.
       (*b*) Carotid sinus reflexes
  2. Reflexes originating in different parts of body, especially
       (*a*) Those arising in abdominal viscera
       (*b*) Pulmocoronary reflex

3. Reflexes originating centrally

(*B*) Extracardiac Reflexes Affecting Coronary Flow

Failure of adequate emptying of depot organs (liver, spleen, skin, etc.)

1. Digestive state
2. Variations in temperature
3. Relaxed abdominal musculature

IV. Humoral Factors

1. Epinephrine
2. Histamine
3. Acetylcholine
4. Vasopressin, etc.

MECHANICAL FACTORS

1. *Fall in Aortic Blood Pressure.*—In the denervated heart-lung preparation of the dog an increase in the mean blood pressure from 50 to 130 mm. of mercury may increase the coronary flow from 20 to 250 cc. per minute.[15] Conversely, a marked fall in the head pressure in the aorta will cause a great decrease in the coronary flow. A reduction of the coronary flow resulting from a severe fall in the aortic pressure may produce anginal pain and, conceivably, myocardial infarction from anoxia. Saphir and his co-workers[16] believe such falls of intra-aortic blood pressure to be a causative factor of myocardial damage in a heart in which the muscular damage is greater than the associated coronary disease.

Similarly, peripheral shock associated with a fall in the aortic head pressure may seriously impair the coronary flow. In surgical shock, paralytic ileus and other states of peripheral failure, anginal pain and coronary thrombosis are not uncommon occurrences. In many cases, furthermore, the cardiac symptoms appear for the first time. At necropsy the myocardial damage is often greater than the associated coronary arteriosclerosis. While direct clinical evidence is difficult to obtain, experimental evidence supports the view that shock may be a causative factor in cardiac ischemia. If a guinea pig is strapped upright to a board, collapse results owing to pooling of blood in the abdomen and lower extremities.[17] Electrocardiograms taken at this time show evidence of myocardial damage, and histologic examination reveals multiple necrotic areas in the myocardium, especially in the septum and papillary muscles of the left ventricle. Similar changes have been observed in guinea pigs after doses of histamine sufficient to cause collapse.

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15. Wright, S.: Applied Physiology, ed. 5, New York, Oxford University Press, 1934.

16. Saphir, O.; Priest, W. S.; Hamburger, W. W., and Katz, L. N.: Coronary Thrombosis and the Resulting Myocardial Changes, Am. Heart J. **10**:567, 1935.

17. Meessen, H.: Ueber Coronarinsuffizienz nach Histamincollaps und nach orthostatischem Collaps, Beitr. z. path. Anat. u. z. allg. Path. **99**:329, 1937.

2. *Phasic Variations in the Coronary Flow.*—Aside from the mean aortic pressure, phasic variations in the coronary flow during both systole and diastole are of the utmost importance.[18] In the normal heart the coronary flow is greater during diastole, since this is the longer phase of the cardiac cycle.[19] Furthermore, the resistance to flow in the coronary arteries arises during systole, as the intramural coronary arteries are compressed by the contracting cardiac muscle. However, even in the normal heart the systolic coronary flow is important, and in pathologic states in which the diastolic pressure is decreased, the systolic coronary flow may provide the major nutrition of the heart.[20]

H. D. Green [20] has shown experimentally that in conditions associated with low diastolic blood pressure, such as aortic insufficiency and arteriovenous fistula, the coronary flow is greatly diminished owing to the low aortic diastolic pressure. This decrease is partly compensated for by elevation of the systolic pressure. An increase in the systolic pressure results in two divergent effects. The increased aortic pressure tends to increase the coronary flow, whereas increased compression of the intramuscular arteries tends to decrease the coronary flow. However, as the systolic pressure is raised, the former outweighs the latter, and the coronary flow is increased. The systolic coronary flow may be increased to double that occurring normally during diastole. In patients with compensated aortic insufficiency, an adequate coronary flow is maintained by reflex peripheral vasoconstriction which elevates the systolic pressure. Failure or inadequacy of this compensatory mechanism may initiate severe myocardial anoxemia.

In aortic stenosis the coronary flow is reduced chiefly during systole. Because of the high intraventricular pressure during systole, there is marked compression of the intramuscular coronary arteries, so that the coronary flow is impeded. In contradistinction to aortic insufficiency, peripheral vasoconstriction would not be a compensatory mechanism. A reflex reduction of the cardiac rate would, however, augment the coronary flow by prolonging the diastole.

Probably the incidence of anginal attacks in young rheumatic patients is related to these phenomena. If the impairment of nutrition is great enough, particularly if there is superadded arrhythmia, the result of disturbances of reflex control, even a fatal outcome, is not uncommon in association with unobstructed coronary arteries.

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18. Gregg, D. E.; Green, H. D., and Wiggers, C. J.: Phasic Variations in Peripheral Coronary Resistance and Their Determinants, Am. J. Physiol. **112**: 362, 1935.

19. Anrep, G. V., and Segall, H. N.: The Regulation of the Coronary Circulation, Heart **13**:239, 1926.

20. Green, H. D.: Coronary Blood Flow in Aortic Stenosis, in Aortic Insufficiency and in Arterio-Venous Fistula, Am. J. Physiol. **115**:94, 1936.

In hypertensive patients, the diastolic and to a lesser extent the systolic coronary flow are augmented by increased systolic and diagnostic pressures.[21] The benefit of an increased systolic and diastolic coronary flow is, however, evanescent, since the underlying cause persists and requires the heart to do an increased amount of work.

3. *Cardiac Hypertrophy.*—Cardiac hypertrophy may result also in impairment of nutrition owing to the increased amount of tissue nourished by the given vascular bed. In addition, the fiber is thicker than normal. Hill [22] showed that the rate of diffusion of oxygen varies inversely as the square of the distance. Gross and Spark [23] observed an inverse ratio between the number of capillaries and the thickness of the fiber. The part of the fiber nearest a capillary will receive ample blood, while the innermost part of the fiber will suffer from anoxia. Harrison [24] demonstrated that in various species of animals the heart rate is in inverse proportion to the size of the cardiac fiber but that in the hypertrophied heart the pulse rate is not proportionately slowed. It has, furthermore, been shown that for a given minute volume, the consumption of oxygen is greater per beat but less per minute at slow than at fast pulse rates.[25] In the thickened fiber, unless diastole is prolonged by a slow pulse rate, anoxia of the cardiac muscle readily develops. Since the oxygen need is greater, the nutritional reserve in the hypertrophied heart is less than that in the normal heart. It is understandable, therefore, that in the enlarged heart with an impaired nutritional reserve, ischemia from any cause may result in myocardial failure, while in the small heart, only transitory anginal pain will occur.

4. *Tachycardia.*—In tachycardia the coronary flow diminishes owing to shortening of the diastole. Gregg [21] showed that the systolic flow is also reduced by tachycardia owing to abbreviation of the systole as well as to increased intramural resistance. In experimental hyperthyroidism and mechanically induced tachycardia, Menne, Jones and Jones [26] noted a parallelism between the increased heart rate and the myocardial lesions.

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21. Gregg, D. E.: Phasic and Minute Coronary Flow During Acute Experimental Hypertension, Am. J. Physiol. **114**:609, 1936.

22. Hill, A. V.: Diffusion of Oxygen and Lactic Acid Through the Tissues, Proc. Roy. Soc., London, s.B **41**:104, 1929.

23. Gross, H., and Spark, C.: Coronary and Extracoronary Factors in Hypertensive Heart Failure, Am. Heart J. **14**:160, 1937.

24. Harrison, T. R.; Ashman, R., and Larson, R. M.: Congestive Heart Failure: Relation Between the Thickness of the Cardiac Muscle Fiber and the Optimum Rate of the Heart, Arch. Int. Med. **49**:151 (Jan.) 1932.

25. Patterson, S. W., and Starling, E. H.: On the Mechanical Factors Which Determine the Output of the Ventricles, J. Physiol. **48**:356, 1914.

26. Menne, F. R.; Jones, O. N., and Jones, N. W.: Changes in the Myocardium of Rabbits from Augmenting the Heart Rate Mechanically and from Induced Hyperthyroidism, Arch. Path. **17**:233 (March) 1934.

In the hypertrophied heart with a limited oxygen and nutritional reserve, tachycardia will produce failure and more marked myocardial damage than in the normal-sized heart. Conversely, the bradycardia seen in some hypertensive patients probably acts as a compensatory mechanism to increase the coronary flow during diastole.

CHANGES IN THE BLOOD

Anemia also causes a compensatory tachycardia and frequently cardiac dilatation. The circulation time is simultaneously shortened. From severe anemia, however, myocardial fibrosis has been known to develop. Büchner and von Lucadou [27] showed that if an animal is rendered anemic by bleeding and then exercised, myocardial fibrosis is more diffuse and electrocardiographic changes are more marked than if the animal is only bled. The occurrence of tigering, fatty infiltration of the myocardium and fibrosis in severe anemia is direct evidence of local want of oxygen.

Polycythemia may produce anoxemia owing to oxygen unsaturation, an increased number of cells and increased viscosity. The tendency for thrombosis to develop in this disease is well known.

REFLEX FACTORS

Despite considerable experimental work, there is no unanimity of opinion concerning the mechanism or the importance of the reflex control of the coronary arteries. This is in part due to the technical difficulty of dissociating vasomotor effects from such factors as heart rate and blood pressure, which also influence the coronary flow. Other factors are the dependence of the reaction on the severity of the stimulus and the fact that different parts of the same coronary vessel vary as to reaction.

When the oxygen need of the myocardium is increased, failure of compensatory reflex dilatation may lead to insufficiency of the oxygen supply. Such failure may result from two situations: 1. The compensatory reflex may for some reason fail to occur or may be inadequate or pathologic changes, such as sclerosis, in the vascular wall may prevent adequate dilatation. 2. In addition to failure of compensatory dilatation, vasoconstriction or its extreme form spasm may play a role in the production of myocardial ischemia. Although most vasomotor coronary reflexes produce dilatation, it is conceivable that in certain pathologic states, reflex spasm may occur.

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27. Büchner, F., and von Lucadou, W.: Elektrokardiographische Veränderungen und disseminierte Nekrosen des Herzmuskels bei experimenteller Coronarinsuffizienz, Beitr. z. path. Anat. u. z. allg. Path. **93**:169, 1934.

Ricker [28] has assumed that the terminal vascular segments form more or less autonomous functional units which react typically to nervous impulses. Weak stimulation produces vasodilatation, medium stimulation produces vasoconstriction and strong stimulation produces excessive vasodilatation and paralysis, while the proximal portions of the arteries remain constricted or the entire vessel becomes dilated. In the highest degree this mechanism leads to stasis, during which the circulation is actually at a standstill. During this state, necrosis of the involved portion of the organ may conceivably occur. Lange [29] demonstrated complete paralysis of arterial segments following strong electrical stimuli and stasis in the vasa vasorum of the adventitia resulting in necrosis of the musculature of the media. He demonstrated intimal proliferation in the poststatic period following exudation.

Coronary Vasomotor Reflexes.—1. Reflexes Originating in the Heart and Associated Structures: Important vasomotor reflexes adapt the coronary flow to the increased work of the heart. Such proprioceptive reflexes originating in the heart and great vessels produce coronary dilatation probably by vagal inhibition and are especially important in adapting the coronary flow to the increased physical work and to cold. That vagal inhibition is the cause of such dilatation is proved by the fact that the effect is lost after vagotomy but not after stellate ganglionectomy.[19] The reaction makes possible an increase of the minute flow and is independent of changes in the diastolic blood pressure. Failure of this reflex mechanism could conceivably produce myocardial ischemia.

An increased cerebral blood supply, according to Anrep and Segall,[19] results in a decreased coronary flow. This reflex, according to Stella,[30] is governed by the carotid sinus. Reduction of the carotid sinus pressure augments the coronary flow.

2. Reflexes Originating in Different Parts of the Body: A variety of vasomotor coronary reflexes originate in widely distributed regions of the body. C. W. Greene [31] has studied these reflexes and has mentioned the universality with which stimulation in different parts of the body produces coronary dilatation. Mild stimulation and stimulation within physiologic limits result in coronary dilatation, with vasocon-

28. Ricker, G.: Pathologie als Naturwissenschaft—Relationspathologie—für Pathologen, Physiologen, Mediziner und Biologen, Berlin, Julius Springer, 1924.

29. Lange, F.: Studien zur Pathologie der Arterien, insbesondere zur Lehre von der Arteriosklerose, Virchows Arch. f. path. Anat. **248**:463, 1924.

30. Stella, G.: Some Observations on the Effect of Pressure in the Carotid Sinus upon the Arterial Pressure and upon the Coronary Circulation, J. Physiol. **73**:45, 1931.

31. Greene, C. W.: Control of the Coronary Flow by Reflexes Arising in Widely Distributed Regions of the Body, Am. J. Physiol. **113**:399, 1935.

striction elsewhere. Wiggers [32] concluded that these somatic and visceral reflexes represent a provision for reducing the coronary resistance in conditions like pain and injury which would otherwise lower the blood pressure and decrease the coronary flow. Greene [31] has also noted that coronary vasomotor reflexes are often diphasic, so that the intial reflex dilatation may be followed later by constriction. An exaggerated constrictor response following dilatation may easily lead to cardiac ischemia. It is noteworthy that profound stimulation directly leads to marked coronary constriction which is independent of general systemic vascular reactions. Such responses must be regarded as pathologic.

Of particular interest are coronary vasoconstrictor reflexes originating in abdominal viscera. Disease of abdominal viscera, especially the gallbladder, is often accompanied clinically by an anginal syndrome. Occasionally the anginal syndrome as well as electrocardiographic signs disappear after cholecystectomy. Similarly, diaphragmatic hernia at the hiatus, as von Bergmann [33] has shown, often produces a clinical picture of coronary disease. The anginal symptoms probably represent true myocardial anoxia secondary to stimulation of an abdominal viscus. Sudden death, which sometimes occurs, may be due to cardiac standstill resulting from extreme vagal stimulation, but it is also possible that such vagal stimulation may produce reflex coronary vasoconstriction and myocardial ischemia.

Scherf and Schönbrunner [34] and others show that strong stimuli originating in the lungs, such as those in pulmonary embolism, may give rise to the so-called pulmocoronary reflex, resulting in cardiac ischemia from reflex coronary vasoconstriction. Hochrein and Keller [35] demonstrated that in pulmonary embolism there is a diminished outflow from the right coronary artery. Electrocardiographic changes typical of those of myocardial injury result from experimental pulmonary emboli, not large enough, however, to cause a significant reduction in the pulmonary blood flow. The effect seems to be mediated through the vagus nerve, for in rabbits, according to Radnai and Mosonyi,[36] the phenomenon is abolished by bilateral vagotomy. The view of McGinn and

32. Wiggers, C. J., in Levy, R. L.: Diseases of the Coronary Arteries and Cardiac Pain, New York, The Macmillan Company, 1937.

33. von Bergmann, G.: Das "epiphrenale Syndrom:" Seine Beziehung zur Angina Pectoris und zum Kardiospasmus, Deutsche med. Wchnschr. **58**:605, 1932.

34. Scherf, D., and Schönbrunner, E.: Ueber den pulmocoronaren Reflex bei Lungenembolien, Klin. Wchnschr. **16**:340, 1937.

35. Hochrein, M., and Keller, J.: Untersuchungen am Koranarsystem, Arch. f. exper. Path. u. Pharmakol. **159**:300, 1931.

36. Radnai, P., and Mosonyi, L.: Ueber den Gefässverengernden Pulmocoronarreflex, Ztschr. f. d. ges. exper. Med. **98**:651. 1936.

White [37] that these changes are secondary to dilatation of the right side of the heart is not plausible, since this dilatation of itself does not produce the same electrocardiographic pattern. The occurrence clinically and electrocardiographically of a coronary symptom complex in pulmonary embolism in human beings is best explained by the pulmocoronary reflex.

3. Reflexes Originating Centrally: Another mode of coronary vasomotor activity is that occurring with central vasomotor stimulation. There are probably a variety of effective stimuli, of which at least one, carbon dioxide acting centrally, produces coronary vasoconstriction.

Extracardiac Reflexes Affecting the Coronary Flow.—We have dealt so far with reflex vasomotor phenomena directly affecting the coronary arteries. The coronary flow is, however, passively altered by reflex phenomena in other organs, notably the liver, spleen and skin, which normally under conditions of increased myocardial oxygen need yield blood to the heart and other organs and may properly be called depot organs. The importance of the depot organs may be fully understood when it is appreciated that 1,500 cc. of blood may be locked in the liver by the contraction of the hepatic veins. Sympathetic stimulation, epinephrine and ephedrine dilate the hepatic veins and aid in the surrender of blood from the liver and other depot organs. Histamine, on the other hand, constricts these veins. The peripheral failure from collapse due to doses of histamine is probably in part the result of constriction of the hepatic veins, which further pools the blood in the splanchnic bed. Closure of the veins of the blood depot organs or their failure to open may, according to Lichtwitz,[38] produce myocardial anoxia and an anginal syndrome.

Conditions in which the depot organs do not readily surrender blood to increase the venous return cause a relative myocardial insufficiency of oxygen; such a situation is the digestive state, and the frequency of coronary attacks after a heavy meal, especially in association with physical effort, is probably related to this fact. The frequent enlargement of the liver and spleen in anginal attacks is indicative of the role of the depot organs. Cutaneous vasodilatation under conditions of heat may act similarly. Anginal seizures on exposure to cold or after a meal are more understandable on the basis of a disturbed blood supply than on the basis of coronary spasm.

Finally, the condition of the abdominal musculature, by altering the intra-abdominal pressure, also plays a role in maintaining the circulation

37. McGinn, S., and White, P. D.: Acute Cor Pulmonale Resulting from Pulmonary Embolism: Its Clinical Recognition, J. A. M. A. **104**:1473 (April 27) 1935.

38. Lichtwitz, L.: Pathologie der Funktionen und Regulationen, Leiden, A. W. Sijthoff's Uitgeversmaatschappij N. V., 1937.

of the heart. The emptying of the blood depots is facilitated by a strong abdominal musculature, which aids the venous return from the splanchnic area during descent of the diaphragm.

HUMORAL FACTORS

The importance of humoral factors in the coronary circulation has been well demonstrated. Of great importance is epinephrine, a powerful constrictor which affects through its peripheral action the sympathetic nervous system. The effect of epinephrine on the coronary arteries is debatable, since some observers have reported constriction and others dilatation. It has been shown that epinephrine may precipitate anginal seizures and that it predisposes to left ventricular failure.[39] Whether the effect is due to a direct action on the heart, an elevated blood pressure, tachycardia or a specific action on the coronary arteries cannot be stated.

Additional humoral agents are histamine and the vasopressor substance of the posterior lobe of the pituitary gland. The predominant action of histamine is a constrictor effect on the arterioles and a dilator effect on capillaries. Vasopressin acts directly on smooth muscle, constricts the arterioles and probably constricts the coronary arteries. In experimental hypertension, such as that produced by Goldblatt,[40] a vasopressor substance is considered to be produced by the ischemic kidney. The action of this humoral substance on the coronary arteries is not known.

Another endogenous agent, acetylcholine, produces marked arteriolar and capillary dilatation. In the coronary arteries, however, the experimental evidence suggests that acetylcholine causes coronary constriction. Hall, Ettinger and Banting [41] produced experimental coronary thrombosis and myocardial damage in dogs by prolonged injection of dilute solutions of acetylcholine. In older animals, changes in the arterial wall, thrombosis and myocardial infarction were encountered, while in young dogs myocardial damage occurred without coronary thrombosis. By stimulation of the vagus nerve alone they produced diffuse myocardial degeneration, small infarcts and subendocardial hemorrhages, together with electrocardiographic changes. Vagal stimulation in dogs to which physostigmine had been given resulted in more extensive cardiac lesions. These experiments indicated the development of organic disease solely from humoral stimulation.

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39. Smith, F. M., in Levy, R. L.: Diseases of the Coronary Arteries and Cardiac Pain, New York, The Macmillan Company, 1937.

40. Goldblatt, H.; Lynch, J.; Hanzal, R. F., and Summerville, W. W.: Production of Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischemia, J. Exper. Med. **59**:347, 1934.

41. Hall, G. E.; Ettinger, G. H., and Banting, F. G.: An Experimental Production of Coronary Thrombosis and Myocardial Failure, Canad. M. A. J. **34**:9, 1936.

OTHER FACTORS

The concept of temporary functional disturbance in angina pectoris is supported by clinical as well as by experimental transitory anginal seizures. Such transitory seizures are sometimes accompanied by temporary electrocardiographic changes. Brow and Holman,[42] Feil and Siegal [43] and Wood and Wolferth,[44] by experimental transient coronary constriction, demonstrated alterations of the terminal deflections of the electrocardiogram, which returned to normal when adequate oxygenation was restored. These observers, as well as Parkinson and Bedford [45] and Hall,[46] reported electrocardiographic changes in patients with transitory anginal seizures simulating those of the early stages of cardiac infarction. They concluded that changes in the ST portion of the electrocardiograms of patients with angina pectoris represent transient vascular changes in the heart. The electrocardiographic changes in experimental cardiac ischemia may appear and disappear within two minutes, a period comparable to that of an anginal attack in a human being. If in the experimental animal, however, the clamp on the coronary artery is left on long enough, cardiac infarction results which is similar to that in man with acute coronary thrombosis.

Transient anginal pain and cardiac infarction affect the electrocardiogram similarly. Since paroxysmal pain cannot be explained solely in terms of morbid anatomy, which is frequently the same as before, during and after the anginal seizure, it seems reasonable to regard the anginal attack even in many patients with organic coronary involvement as due to a transient disturbance of function. The mechanisms underlying both the electrocardiographic changes and the pain are probably the same whether the anoxemia is short and produces reversible myocardial change or is prolonged and results in permanent myocardial damage.

In the brain, which is functionally similar to the heart in many ways, it has also been shown that functional factors may play a significant role

42. Brow, G. B., and Holman, D. V.: Electrocardiographic Study During a Paroxysm of Angina Pectoris, Am. Heart J. **9**:259, 1933.

43. Feil, H., and Siegal, M. L.: Electrocardiographic Changes During Attacks of Angina Pectoris, Am. J. M. Sc. **175**:255, 1928.

44. Wood, F. C., and Wolferth, C. C.: Angina Pectoris: The Clinical and Electrocardiographic Phenomena of the Attack and Their Comparison with the Effects of Experimental Temporary Coronary Occlusion, Arch. Int. Med. **47**:339 (March) 1931.

45. Parkinson, J., and Bedford, D. E.: Electrocardiographic Changes During Brief Attacks of Angina Pectoris, Lancet **1**:15, 1931.

46. Hall, D.: Electrocardiograms of Two Patients During Attacks of Angina Pectoris, Lancet **1**:1255, 1932.

in producing organic disease. Spielmeyer [47] has shown that functional spasm of the cerebral vessels may cause an impairment of nutrition resulting in degeneration of the central nervous system. After epileptic seizures he observed fresh changes in the brain which he thought due to temporary circulatory impairment. His colleague Neubürger [48] found recent destruction of cardiac muscle after epileptic seizures.

A variety of physiologic mechanisms, derangements of which may lead to myocardial anoxia or even infarction, have been discussed. Many of these, more specifically those which do not directly involve localized vascular areas, have a generalized effect on the heart. Profound disturbances of these, it would be expected, would lead to generalized pathologic changes in the myocardium rather than to localized infarcts, such as existed in our cases. This objection is minimized by certain considerations. First, while the disturbance may be generalized, the most severe and irreversible pathologic changes would occur in the areas of greatest functional stress. The end result might therefore appear as a localized lesion. Secondly, experimental evidence supports this concept. In the experiments on orthostatic collapse produced by maintaining a guinea pig in the vertical position, the myocardial anoxia is undoubtedly generalized. Nevertheless, the lesions are preponderant in certain areas. Other experiments, like the injections of acetylcholine previously mentioned, also produce preponderantly localized lesions.

Finally, it is conceivable that certain local factors in the myocardium may produce specific effects on associated vessels and thus intensify the disturbance in a given area. With myocardial anoxia there is a local increase in carbon dioxide, lactic acid, phosphoric acid and other metabolites, with a lowering of the p_H. These factors as well as oxygen lack per se tend to dilate the coronary arteries. However, with the increase in vascular permeability and the alteration of chemical equilibrium due to ischemia, edema results which affects the walls of the vessels themselves as well as the myocardium.

As far back as 1912, Klemensiewicz,[49] who studied the relation of edema to ischemia, stated that in the course of ischemia changes in permeability may occur in the vascular wall leading to localized edema of the wall which may go on to irreversible organic lesions. Thrombosis, if it occurs after such changes in the wall, may be the result rather than

47. Spielmeyer, W.: Influence of Functional Circulatory Disturbances on the Central Nervous System, J. Nerv. & Ment. Dis. **71**:293, 1930.

48. Neubürger, K.: Herz, Epilepsie, Angina pectoris, Klin. Wchnschr. **12**:1355, 1933.

49. Klemensiewicz, R.: Die Pathologie der Lymphströmung, in Krehl, L., and Marchand, F.: Handbuch der allgemeinen Pathologie, Leipzig, S. Hirzel, 1912, vol. 2, p. 341.

the cause of myocardial ischemia. It seems reasonable to postulate that if the edema of the vascular wall is of sufficient severity to produce necrosis of the myocardium but not to produce irreversible changes in the vessel, subsequent examination may show destruction of the cardiac muscle without corresponding damage to the vascular wall.

It follows that there is no strict separation between the cases in which there is a functional disturbance and those in which there is organic thrombosis. A physiologic approach to the problem provides a more satisfactory interpretation of the wide diversity of clinical and anatomic features in cases ranging from those of purely functional disorders to those of advanced organic coronary disease.

SUMMARY AND CONCLUSIONS

Fifteen cases of myocardial infarction without demonstrable occlusion of the coronary arteries were studied. Arteriosclerosis of the coronary arteries was minimal. In 1 case all the major vessels were sectioned serially.

A variety of physiologic mechanisms which might account for myocardial damage in the absence of vascular occlusion is outlined. These may be mechanical, reflex or humoral: 1. Mechanical factors include temporary falls in intra-aortic blood pressure, tachycardia, phasic variations of the coronary flow and cardiac hypertrophy. Changes in either the number of formed elements or the viscosity of the blood, such as are seen in anemia and polycythemia, are contributory factors. 2. Reflex factors may produce anoxia of the myocardium from failure of adequate compensatory dilatation of the coronary arteries or from coronary constriction. The stimuli for these reflexes may arise either in the heart and its associated structures or in other parts of the body. 3. Humoral factors and possibly other agents, including acetylcholine, epinephrine and vasopressin, also alter the caliber of the coronary arteries.

The presence of hypertension in 13 of our 15 cases is of great interest. Vasoconstrictor phenomena are common in hypertension, and it is conceivable that extreme coronary vasoconstriction may have played a role.

The underlying cause of the anginal seizure, whether transitory or associated with myocardial infarction, is ischemia of the myocardium. Similarly, the electrocardiographic changes in both instances are also the result of myocardial ischemia. The duration of ischemia will determine whether the cardiographic and myocardial changes are reversible or not.

Though the occurrence of the type of case reported by us is infrequent, it is nevertheless of importance, since similar physiologic factors must also play a role in many cases of ordinary coronary disease and myocardial damage.

HEMOLYTIC JAUNDICE

IMMEDIATE AND DELAYED CHANGES IN THE BLOOD AFTER SPLENECTOMY

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OMAHA

That splenectomy causes a "clinical cure" of hemolytic jaundice has been well known for some time, but only recently has our attention been called to the immediacy of the changes in the blood that follow the operation.[1] In the past four years 26 cases of typical familial hemolytic jaundice have been observed,[2] in 12 of which the spleen was removed without fatality. Eight of the splenectomized patients have been subjected to careful detailed study with special reference to changes occurring in the blood during and immediately after splenectomy. It is our purpose to present the results of this study together with control observations on 5 additional cases of "refractory" anemia in which splenectomy was performed. We hope that our additional information concerning the action of the spleen will be of some clinical value to the physician in his understanding and handling of the patient with hemolytic jaundice.

METHODS

In this group of 8 cases, the diagnosis of hemolytic jaundice was made without question from the detailed individual history and family history, a careful physical examination and complete and thorough hematologic studies, which included blood counts, hematocrit studies, erythrocytic fragility tests, reticulocyte counts and determinations of the icterus indexes and van den Bergh reactions. The period of control observation before splenectomy varied in different instances from a few

From the Department of Medicine and the Department of Surgery, the University of Nebraska College of Medicine.

1. Doan, C. A.; Wiseman, B. K., and Erf, L. A.: Studies in Hemolytic Jaundice, Ohio State M. J. **30**:493-504 (Aug.) 1934. Doan, C. A.; Curtis, G. M., and Wiseman, B. K.: The Hematolytopoietic Equilibrium and Emergency Splenectomy, J. A. M. A. **105**:1567-1575 (Nov. 16) 1935. Curtis, G. M.; Doan, C. A., and Wiseman, B. K.: Splenectomy for Hemolytic Crises, Ann. Surg. **104**:892-903 (Nov.) 1936.

2. Sharpe, J. C.: Hemolytic Jaundice, Internat. Clin. **2**:146-167 (June) 1937.

weeks to many months. Additional laboratory and roentgen studies were made, but the results are not important in the consideration of this particular problem. The patients were all white. There were 7 females and 1 male. Their ages varied from 4 to 42 years.

The patients were hospitalized several days prior to operation, and complete studies of the blood were made daily. On the day of operation certain studies [3] were made before the anesthetic was administered, during surgical manipulation of the spleen but before ligation of its pedicle and at fifteen minute periods thereafter during the remainder of the operation. The samples of blood were obtained from a stab puncture of the finger tip. These same studies were carried out two, four, eight, twelve, twenty-four and forty-eight hours after operation and every three to five days thereafter during hospitalization. Routine checks of the blood counts were made at varying intervals every one to three months after splenectomy.

The operations were purposely performed with various types of anesthesia, including spinal anesthesia and anesthesia induced with cyclopropane, nitrogen monoxide and ether, and avertin with amylene hydrate and ether. For the most part the surgical approach and technic of Wilkie [4] were used. In this group, neither transfusions nor any other type of antianemic therapy was given either preoperatively or postoperatively, so that any change in the blood picture was considered directly attributable to the splenectomy.

With the same plan of study, a group of control observations were made on 5 patients with severe refractory anemia before, during and after splenectomy. The patient in case 1 was a woman 21 years of age; the remaining patients were older, 2 men and 2 women whose ages varied from 52 to 64 years. All had marked and persistent anemia, acholuric jaundice, reticulocytosis, hyperplasia of the bone marrow and gross splenomegaly for which, even after complete postmortem examinations in 3 of the 5 cases, the cause could not be clearly established. Splenectomy was tried only after a long period of observation in which all forms of medical therapy to combat the anemia had failed. These patients differed from those with typical hemolytic jaundice in that there was no evidence of a familial tendency, the blood picture was characterized by an absence of spherocytosis, and the fragility, though slightly altered, was not definitely increased. The patient in case 4 died on the third postoperative day, of thrombosis of the splenic vein; [5] the patient in case 2 died of postoperative pneumonia one week after splenectomy; the patient in case 3 died as the result of postoperative hemorrhage following a subsequent cholecystectomy nine months after splenectomy. The patients in cases 1 and 5 were living twelve and seven months after splenectomy, but in neither case had the clinical or the hematologic picture changed from that observed prior to operation. At a later date this group of cases of atypical hemolytic anemia, recently referred to by Thompson,[6] will serve as the basis of a detailed report on the controversial question of the "acquired" or refractory type of hemolytic anemia.

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3. Erythrocyte, leukocyte, differential and reticulocyte counts and determinations of the icterus index and the hemoglobin content of the blood.

4. Wilkie, D. P. D.: Splenectomy: Its Indications and Technique, Am. J. Surg. **14**:340-355 (Oct.) 1931.

5. Davis, H. H., and Sharpe, J. C.: Splenic Vein Thrombosis Following Splenectomy, Surg., Gynec. & Obst. **41**:678-682 (Nov.) 1938.

6. Thompson, W. P.: Hemolytic Jaundice: Diagnosis, Behavior and Treatment, J. A. M. A. **107**:1776-1781 (Nov. 28) 1936.

RESULTS

Hemoglobin.—In the group of 8 cases of typical hemolytic jaundice, the value for hemoglobin at the time of operation in 5 cases was 70 per cent or below, while in the other 3 cases it ranged from 82 to 96 per cent

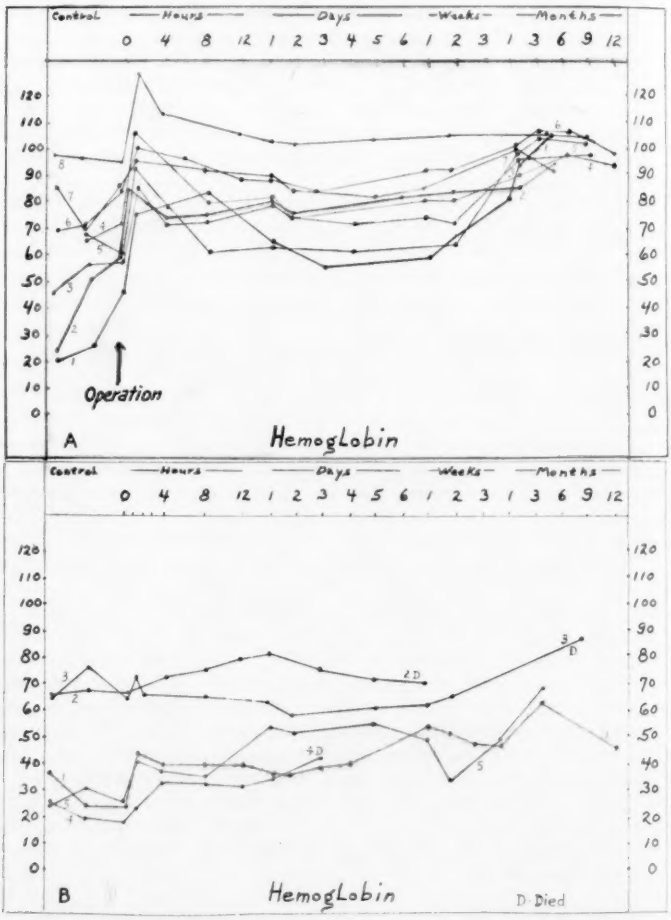

Chart 1.—*A*, hemolytic jaundice; *B*, atypical hemolytic anemia.

(chart 1 *A*). From the time the anesthetic was given to the point of ligation and cutting of the splenic pedicle there was a necessary ten to twenty minute interval of handling, manipulating and squeezing the spleen during the process of freeing the organ from adhesions and its normal ligamentous attachments. During this period, in each of the 5

cases of severe anemia there was a sharp rise in the hemoglobin content of the blood, varying from 16 to 32 per cent. There was no appreciable change, however, in cases 6, 7 and 8, in which the control hemoglobin determinations were within normal limits. After the splenic pedicle was ligated and the spleen removed, the hemoglobin continued to increase slightly (3 to 12 per cent) during the first postoperative hour in the first 5 cases and more sharply (10 to 28 per cent) in the remaining 3 cases. In other words, at the end of the first hour after splenectomy the hemoglobin had increased in every case from 10 to 35 per cent, with the astounding average of 23.2 per cent for the group. From our observations, it would seem that the lower the preoperative hemoglobin level, the more rapid and more marked the increase, the change occurring, for the most part, during actual surgical manipulation of the spleen. There seemed to be no direct relation, however, between the size of the spleen and the degree of change occurring in the blood during its removal.

After the sudden increase of hemoglobin during the operation and the first hour after the operation, there was a slow but definite drop during the first eight hour period, the decrease varying from 3 to 33 per cent and averaging 16 per cent for the group. The decrease in hemoglobin continued in most cases to about the third postoperative day, and though it approached, in no instance did it actually return to, the preoperative level. During the remainder of the first week after removal of the spleen, although the chart shows a definite "leveling off" with little or no change in the amount of hemoglobin, the patient showed a daily clinical improvement associated with a rapid return to normal of the reticulocyte count and the icterus index. The value for hemoglobin each week thereafter showed a slow but sustained improvement, returning to normal limits by the end of four to eight weeks.

The control series of 5 splenectomized patients with atypical hemolytic anemia showed no such temporary immediate or permanent secondary change in hemoglobin as was uniformly observed in cases of familial hemolytic jaundice (chart 1 *B*). In the 3 cases of this group in which anemia was most severe, manipulation of the spleen during operation caused a rise of 6 to 14 per cent in the first hour, but it in no way compared to that observed in cases of familial hemolytic jaundice. In addition, the subsequent postoperative curve did not show the gradual increase to normal. The 3 patients who survived the first postoperative month showed an average of 57 per cent for the group as compared to their preoperative average of 42 per cent. At the time of writing the 2 remaining living patients, twelve and seven months after removal of the spleen, remain only slightly improved.

Erythrocytes.—At the time of operation, the control red blood cell counts of 7 of the 8 patients with typical familial hemolytic jaundice

were below 4,000,000 per cubic millimeter. Three of them were between 2,000,000 and 3,000,000 cells per cubic millimeter (chart 2 *A*). In case 8 the erythrocyte count was 4,600,000 on the day of splenectomy. Again,

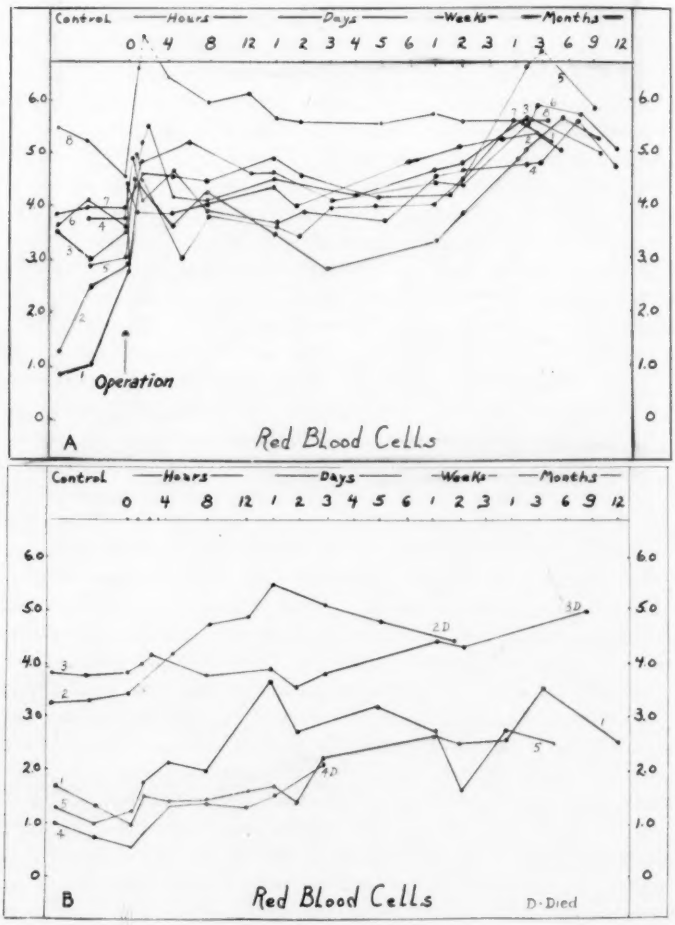

Chart 2.—*A*, hemolytic jaundice; *B*, atypical hemolytic anemia.

irrespective of the red blood cell level at the time operation started, a dramatic response was observed during the short interval of handling the spleen before actual ligation of the pedicle. In this fifteen to twenty minute interval, the increase varied from 200,000 to 1,900,000 cells, the average for the group being 980,000. As observed in the hemoglobin

determinations, the increase of red cells continued, though not as sharply, for one to two hours after the spleen had been removed. Up to this time the average increase for the group from the initial preoperative count was 1,100,000 cells. After the second hour the curve for the group varied somewhat, the count in 4 cases showing a sharp decline, that in 2 continuing to increase slightly for a few more hours and then beginning its descent and that in the remaining 2 "leveling off" for six to twelve hours before showing a decrease. All, however, within the first forty-eight hour period gradually fell to approach their preoperative control determinations.

Though there was some individual fluctuation on the curves during the first week after operation, the trend for the group showed a beginning upward swing that carried each count to approximately 5,000,000 cells by the end of the first month. The patient in case 3 had temporary polycythemia, the erythrocyte count being 7,200,000 three months after operation.

In the group of cases of atypical hemolytic anemia (chart 2*B*) a definite pattern of response to splenectomy was again lacking. No sharp immediate increase of any degree was observed during the operative interval. Although in cases 2 and 5 there were striking increases at the end of twenty-four hours, the counts in both promptly declined to and remained at subnormal levels by the end of the first week. The patients in cases 1 and 5, twelve and seven months respectively after splenectomy, were still moderately anemic.

Leukocytes.—In each case of hemolytic jaundice, splenectomy caused a profound change in the number of leukocytes (chart 3*A*). Before operation the average white cell count for the group was 11,800 per cubic millimeter. After the manipulative phase and before ligation of the splenic vessels, the number of white cells began a steep and rapid ascent. The increase varied from 2,600 to 48,000 cells, the average for the group being 28,300 cells. The rise in the leukocyte count continued during and after the operation, reaching a maximum height in from one to eight hours postoperatively and ranging from 14,000 to 51,250, with an average of 45,800 for the group. The increase was uniformly of the polymorphonuclear series, chiefly the younger forms, the total percentage varying from 89 to 97 at the peak of the increase.

After this rapid initial rise in the leukocyte count there was a slower decrease for the first week after splenectomy, approaching but not returning to the normal levels. This postoperative leukocytosis, with a leukocyte count ranging from 10,000 to 16,000 cells and a normal differential formula, has persisted in each case up to the time of writing.

In the cases of atypical hemolytic anemia (chart 3*B*), with the exception of case 3, the amazing sudden increase in leukocytes did not

occur during the operation. With a much lower preoperative leukocyte count than was observed in the first group, averaging 3,640 cells per cubic millimeter, splenectomy produced only a slight increase in the

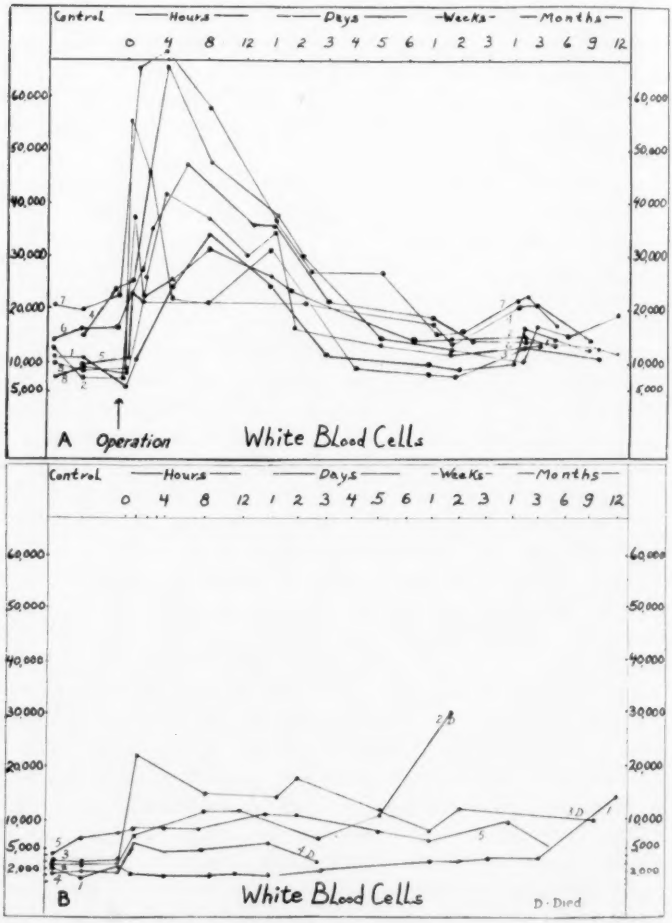

Chart 3.—*A*, hemolytic jaundice; *B*, atypical hemolytic anemia.

number of cells. Except for a leukocyte count of 32,000 observed in case 2, in which the patient succumbed to postoperative pneumonia, the average for the group at the end of the first week after splenectomy was 4,700 white cells per cubic millimeter.

COMMENT

From these observations on the changes occurring in the blood during and after removal of the spleen, two problems naturally present themselves: 1. What are the factors responsible for the production of these unusual changes? 2. Of what clinical use and importance are these changes in considering the patient with hemolytic jaundice?

At present there is almost universal agreement among clinicians that gradual improvement in the red cell level follows splenectomy for hemolytic jaundice.[7] The striking suddenness with which such changes occur was pointed out first by Glover and Fargo [8] and later by Doan and his associates.[1] The latter group found in addition that after splenectomy a major increase, frequently of 1,000,000 or more red cells per cubic millimeter, occurred immediately, before the patient left the operating table. They further stated that studies of the blood volume proved this erythema to be not simply a relative cellular increase dependent on some loss in plasma volume but an immediate, large and significant increase in the actual circulating erythrocytic cell volume. They concluded:

> The disgorgement of the sequestered blood cells from the splenic reservoir incident to operation, and the sudden elimination of the destructive activity of the splenic phagocytes render more effective the unusually active erythropoiesis and erythrocytic delivery that characterize the bone marrow in hemolytic anemia.

Before attempting to explain the results of our observations, it would first be pertinent to review briefly a few of the more recently discovered and important facts concerning the fundamental physiologic action of the spleen. Barcroft [9] has definitely shown experimentally that the spleen acts as a reservoir of red blood corpuscles and that under various influences it is capable of marked alterations in its volume, with resulting changes in the numbers of blood cells in the peripheral circulation. Cruickshank [10] estimated the amount of blood expelled from the spleen by a single contraction to be from 2.6 to 5.6 per cent of the total blood volume of the animal. Miller and Rhoads,[11] in a

7. Cheney, W. F., and Cheney, G.: Chronic Hereditary Hemolytic Jaundice, Am. J. M. Sc. **187**:191-212 (Feb.) 1934. Pemberton, J. D.: Results of Splenectomy in Splenic Anemia, Hemolytic Jaundice, and Hemorrhagic Purpura, Ann. Surg. **94**:755-765 (Oct.) 1931.

8. Glover, D. M., and Fargo, W. C.: Familial Hemolytic Jaundice, Ohio State M. J. **29**:428-432 (July) 1933.

9. Barcroft, J.: Alterations in the Volume of the Normal Spleen and Their Significance, Am. J. M. Sc. **179**:1-30 (Jan.) 1930.

10. Cruickshank, E. W. H.: Output of Hemoglobin and Blood by the Spleen, J. Physiol. **61**:455-464 (June) 1926.

11. Miller, D. K., and Rhoads, C. P.: The Effect of Splenic Contractions on the Formed Elements of the Blood in a Case of Anemia and Splenomegaly, J. Clin. Investigation **12**:1009-1033 (Nov.) 1933.

study of the spleen as a reservoir of blood, reported a case of anemia and splenomegaly in which it was possible to induce marked contraction of the spleen by the parenteral use of various drugs. Accompanying the induced splenic contractions, there occurred within a few minutes marked increases in the number of cellular elements of the circulating blood, amounting to as much as 520,000 red blood cells per cubic millimeter and 15 per cent hemoglobin. Determinations of blood volume after contraction of the spleen showed a slight increase in the total blood volume and a slight reduction of the plasma volume.

From these observations, there seems to be little doubt concerning the capacity of the spleen to act as a storehouse for blood elements and by altering its volume to cause striking changes in the peripheral blood stream. Some of these changes in the blood, however, have been induced in patients without spleens. Patek and Doland [12] made studies of the blood before and after the subcutaneous injection of epinephrine hydrochloride in normal subjects, patients with hemolytic jaundice before and after splenectomy and patients with splenomegaly from miscellaneous diseases. In no case was there any significant change of concentration of red blood cells, in the hematocrit reading or in the hemoglobin. In all cases leukocytosis involving the mature forms of both myeloid and lymphoid cells occurred. Since the changes were not greater in patients with spleens than in splenectomized patients they appeared to be due not to splenic contractions but to a mechanical alteration in the blood stream. Using epinephrine hydrochloride, we had independently made the same observations and come to the same conclusions in a few selected cases both before and after splenectomy.

In order to evaluate any alteration in the blood during and after splenectomy, one must first know what changes, if any, take place during any major operative procedure done under various types of preoperative medication and anesthetics. This problem has been adequately covered by former investigators [13] who, working with a large series of surgical patients whose illness was not complicated by infection or hemorrhage, came to the following conclusions: 1. Slight change or no change in the hemoglobin or red blood cells occurs during or after various operations performed with the aid of local, inhalation or

12. Patek, A. J., and Doland, G. A.: The Effect of Adrenalin Injections on the Blood of Patients With and Without Spleens, Am. J. M. Sc. **190**:14-21 (July) 1935.

13. Mann, F. C.: Some Bodily Changes During Anesthetics, J. A. M. A. **97**: 172-175 (July 15) 1916. Meleney, F. L.: A Study of Anteoperative and Postoperative Blood Counts in Non-Infectious Surgical Conditions, Ann. Surg. **67**: 129-148 (Feb.) 1918. Witter, M. S.: Postoperative Leucocytosis, Surg., Gynec. & Obst. **40**:23-30 (Jan.) 1925. Taylor, I. B., and Water, R. M.: Leucocytosis Following Inhalation Anesthesia, Anesth. & Analg. **14**:276-281 (Nov.-Dec.) 1935.

spinal anesthetics. 2. Leukocytosis occurs, the leukocyte count being two to three times the preoperative count, reaching its peak in four to eight hours and returning to normal numbers at the end of four to five days, with a slight lag of a day or so in the return of the differential formula. Inhalation anesthetics cause a higher increase in the leukocyte count than do anesthetics administered by the spinal route. The increase appears to be due to direct stimulation of the bone marrow and not related to the spleen. We have confirmed these observations on a relatively small number of surgical patients.

The changes in the cellular elements of the blood which occur after transfusion have been studied by Sibley and Lundy.[14] These authors have shown that after a transfusion of 500 cc. of citrated blood, an increase of the value for hemoglobin of from 12.7 to 16.8 per cent (2.12 to 2.8 Gm. per hundred cubic centimeters) can be expected at the end of the second day in those cases in which reactions do not occur and in which bleeding does not follow the transfusion.

With this background it seemed logical for us to use as controls patients with conditions closely allied to hemolytic jaundice, for whom splenectomy was tried as a therapeutic measure. This is especially important when one considers the factor of squeezing and manipulation of the spleen and the question of an autotransfusion effect that would necessarily be absent during any other type of operation.

Turning then to our observations on the group of cases of typical hemolytic jaundice, we may corroborate the conclusion of Doan and his associates [1] that an immediate and dramatic change in the cellular elements of the blood occurs during splenectomy. We have been able to demonstrate, however, that this change is temporary, lasting only a few hours, and it appears to be merely the result of an outpouring of blood cells into the peripheral circulation from an enlarged splenic reservoir that is squeezed and handled during the surgical procedure. In each instance the reduction of splenic size and volume that occurs during operation is visible and obvious.

After splenectomy there is a readjustment of the fluid balance, and the hemoconcentration decreases within forty-eight hours, with subsequent reduction in the number of cells to almost the preoperative level. With removal of the spleen and its destructive effect on the erythropoietic equilibrium, the hyperplastic bone marrow, so characteristic of this specific disease entity, quickly compensates for the reduced numbers of cells and a second and more gradual but permanent increase, this time to normal limits, takes place. This secondary rise in the hemoglobin level and the erythrocyte count appears similar to that seen after

14. Sibley, W. L., and Lundy, J. S.: The Behavior of the Hemoglobin After Blood Transfusion, Surg., Gynec. & Obst. **67**:293-295 (Sept.) 1938.

the reticulocyte shower in pernicious anemia during adequate liver therapy. Three of these original patients have undergone a later cholecystectomy, during which there was no appreciable change in the amount of hemoglobin or the number of erythrocytes, although a moderate but transitory increase in the leukocyte count occurred.

An interesting feature of our observations was the gross difference between the changes in the blood in our cases of typical hemolytic jaundice and those in our cases of so-called atypical hemolytic anemia. If, as we have assumed, the initial changes that occurred in the former group were merely an autotransfusion effect of squeezing an enlarged spleen before its removal, the same dramatic increase should have resulted during splenectomy in the latter group. This, however, was not the case. A possible explanation for this interesting contrast lies in the differences in the histologic appearance of the spleen. In the patients with hemolytic jaundice the spleen was essentially normal histologically, though there was considerable congestion of the splenic pulp. On the other hand, in the second group the sections of the spleen showed little, if any, congestion but frequently showed mild fibrosis and reticular cell hyperplasia with a fairly large number of free histiocytes and nucleated red blood cells. Such a distinct difference in the splenic histologic picture may account for the respective reactions of the elements of the peripheral blood occurring during and after splenectomy. Furthermore, it would seem obvious that splenectomy in cases of refractory anemia has no beneficial effect on the anemia. This problem, together with the peculiar histiocytic reaction observed in the spleens in such cases, will serve as the basis of a future report.

As a result of our experience with the promptness of the changes occurring in the blood during and after splenectomy, we have not hesitated to suggest splenectomy for patients with hemolytic jaundice even in the presence of moderate or severe anemia. In our series of 12 splenectomized patients the results have been uniformly excellent. It is our practice to recommend splenectomy for patients with clinical manifestations of the disease, irrespective of age and independent of the severity of involvement and the presence of complications. In such patients the chronicity of symptoms and the risk of serious complications more than offset the low risk of operation. Although we have had several of our patients under observation during typical hemolytic crises, we have not yet felt it necessary to resort to splenectomy as an "emergency" procedure as advocated by Doan and his associates [1] and therefore have not had the opportunity to observe the response of this type of patient. It would seem, however, that if, with this type of critically ill patient, the first increase of blood occurring during splenectomy were followed by several daily blood transfusions, the subsequent

decrease could be averted to a large degree and the danger of postoperative complications greatly lessened.

SUMMARY

In patients with familial hemolytic jaundice, splenectomy caused dramatic, immediate changes in the blood, which persisted for only a few hours. These primary changes were the result of an autotransfusion effect from surgical manipulation of the enlarged splenic reservoir.

During the first four to six weeks after splenectomy, a second rise, gradual and permanent, to normal limits was observed in the hemoglobin content and the erythrocyte count. This second increase resulted from removal of the destructive function of the spleen, which previously kept these values below normal in spite of a hyperplastic bone marrow.

No comparable blood changes were observed during or after splenectomy in a group of cases of atypical hemolytic anemia, in various general abdominal operations or in splenectomized patients with familial hemolytic jaundice undergoing cholecystectomy.

POLYOSTOTIC FIBROUS DYSPLASIA

REPORT OF A CASE

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The skeletal disease known as polyostotic fibrous dysplasia has been described in the literature under a variety of designations, including osteodystrophia fibrosa unilateralis, osteitis fibrosa localisata, osteodystrophia fibrosa cystica generalisata, fibrous osteodystrophy and osteitis fibrosa disseminata. Since the osseous changes, which in this condition are usually predominantly or exclusively unilateral, simulate roentgenographically those due to hyperparathyroidism (osteitis fibrosa cystica, Recklinghausen's disease of bone), it is essential to exclude the latter disease so that the patient may not be subjected to unnecessary exploration of the neck and thorax. The term "polyostotic fibrous dysplasia" was applied to this condition by Lichtenstein [1] and Jaffe,[2] each of whom described a rather characteristic histologic picture of the bone lesion. The present case is reported because it illustrates certain points of importance in differential diagnosis and because we feel that the possible presence of this disorder is frequently overlooked in cases in which the roentgenographic picture of osteitis fibrosa cystica generalisata is present without definite evidence of hyperparathyroidism.

REPORT OF CASE

H. M., a Polish woman aged 20, was admitted to the Jefferson Medical College Hospital in November 1937, complaining of pain in the regions of the hips and increasing deformity of the thighs of nine years' duration. The latter condition had recurred on the right side despite a corrective osteotomy of the femur performed two years previously at another hospital. On a second admission, in April 1938, the patient complained of diffuse pain in the upper extremities and

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1. Lichtenstein, L.: Polyostotic Fibrous Dysplasia, Arch. Surg. **36**:874 (May) 1938.

2. Jaffe, H. L., in discussion on Garlock, J. H.: The Differential Diagnosis of Hyperparathyroidism, with Special Reference to Polyostotic Fibrous Dysplasia (Lichtenstein-Jaffé), Ann. Surg. **108**:347 (Sept.) 1938.

such severe discomfort and weakness in the lower extremities that she had become bedridden. Her family history and past medical history had no bearing on the present illness.

Physical Examination.—There was marked bowing of the thighs, especially the right, associated with ½ inch (1.3 cm.) shortening of the right lower extremity as compared with the left. There was restriction of motion of both hip joints, due to coxa vara deformities, and considerable tenderness on palpation of the deep tissues of both thighs. Investigation of the genitourinary system and the central nervous system, including studies of the spinal fluid and examination of the eye-grounds and visual fields, revealed no abnormality. The lungs, heart and abdomen appeared normal, and there was no evidence of parathyroid tumor.

Roentgen Examination.—The bones of the skull, thorax and spine and both upper extremities appeared normal.

Pelvis: there were many circular radiolucent areas, varying from the size of a pea to that of a walnut, throughout both iliums and most marked just above the acetabulums, especially on the right side. There were osteoporosis and cortical expansion in the rami of the right ischium and the pubis.

Femurs: Coxa vara and outward bowing deformities were present on both sides, more marked on the right, where there was shortening of the entire bone. There was diffuse osteoporosis with cortical thinning throughout the entire shaft. There was considerable expansion of the upper halves of both femurs. Coarse trabeculations simulated cyst formation. A transverse area of increased density below the right lesser trochanter marked the site of the previous osteotomy.

Tibias and Fibulas: There was diffuse osteoporosis with cortical thinning and expansion throughout the right tibia and the left fibula.

Bones of Feet: A large oval radiolucent area was present in the right os calcis; the right scaphoid and cuneiform bones showed diffuse mottling. There was a fusiform expansion of the shafts of the right fourth and fifth metatarsal bones and broadening of the proximal phalanges of the right fourth and the left second toe (fig. 1).

Laboratory Studies.—Blood Count: Repeated examinations between Nov. 29, 1937 and Sept. 25, 1938 showed hemoglobin ranging from 64 to 96 per cent (Dare), red blood cells from 3,600,000 to 4,850,000 and white blood cells from 6,700 to 11,400. The differential leukocyte count was normal.

Urinalysis: The patient was catheterized and the voided specimens were consistently normal. A twenty-four hour specimen failed to reveal Bence Jones protein.

Calcium and Phosphorus Studies: The following values were recorded.

Date	Serum Calcium, Mg. per 100 Cc.	Serum Phosphorus, Mg. per 100 Cc.	Serum Protein, Mg. per 100 Cc.	Serum Phosphatase Activity, Bodansky Units
Nov. 16, 1937	8.63	3.2	...	8.5
Nov. 29, 1937	....	...	6.4	....
Dec. 3, 1937	....	...	...	10.0
April 28, 1938	11.20	2.2	...	....
May 20, 1938	8.43	2.4	...	6.5
May 27, 1938	9.48	2.1	...	7.8
June 19, 1938	....	...	5.94	....
June 27, 1938	8.78	5.2	6.28	11.2
Sept. 7, 1938	11.0	3.2	7.84	2.7

Urinary excretion of calcium and phosphorus for three day periods with a low calcium diet (0.111 Gm. of calcium and 0.78 Gm. of phosphorus daily) was as follows:

Date	Calcium, Mg.	Phosphorus, Mg.
May 30-June 2, 1937	348	884
June 24-27, 1938	172	2,720
Sept. 4-7, 1938	232	1,523

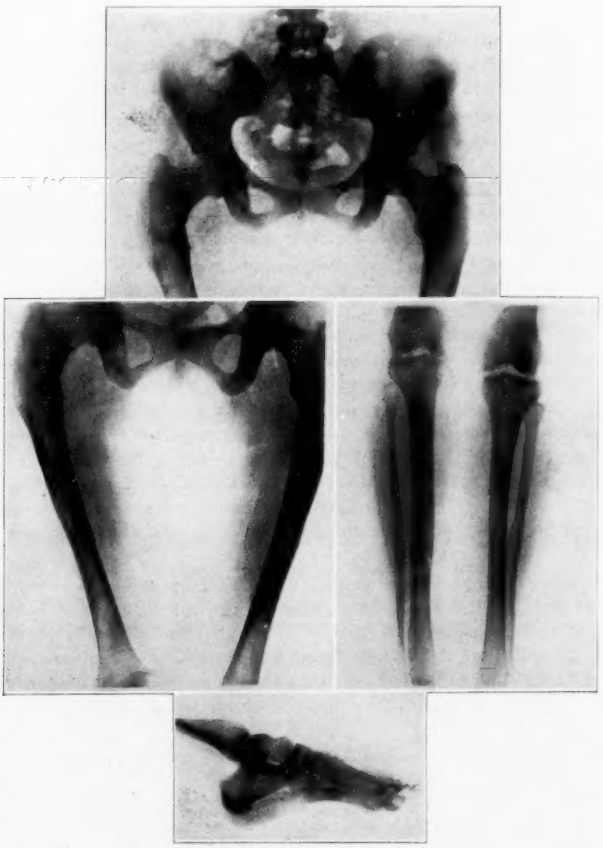

Fig. 1.—Roentgen changes in the bones.

Other Findings: The Wassermann and Kahn reactions of the blood were negative. The cholesterol content of the plasma was 119 mg. per hundred cubic centimeters. The sugar content of the blood was 76 mg. and the urea nitrogen content 10.5 mg. per hundred cubic centimeters. The urea clearance of the blood was 51 per cent of the average normal. The dextrose tolerance was normal. The basal metabolic rate was + 15 per cent in November 1937 and —17 per cent in July 1938.

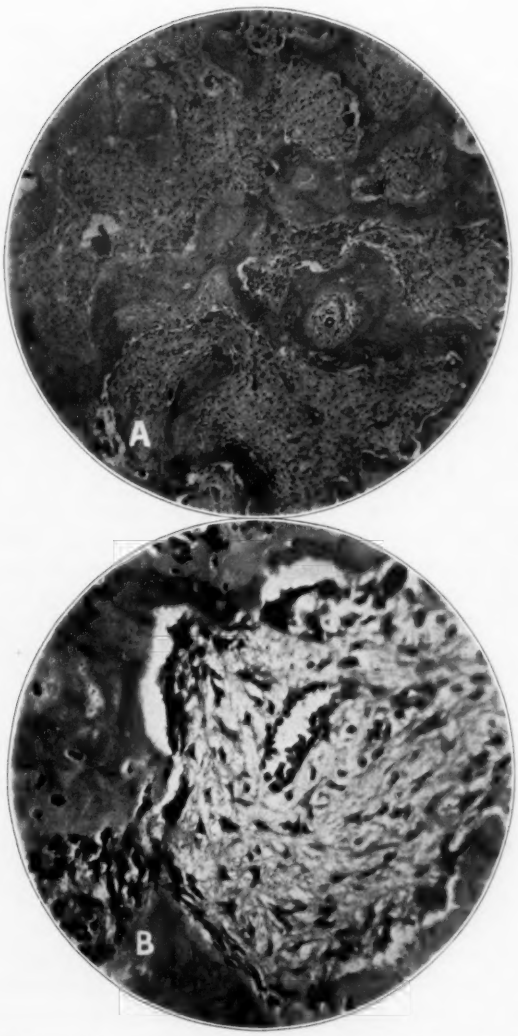

Fig. 2.—Microscopic appearance of biopsy specimen in different magnifications: *A*, × 100; *B*, × 250.

Biopsy of Bone.—On July 5 a piece of bone was removed from the left femur, just below the level of the great trochanter. Grossly, no periosteal reaction was observed; the cortex was extremely thin, and the spongiosa was replaced by a gritty, whitish fibrous tissue which bled slightly. Microscopic examination revealed that the spongy bone had been replaced by, and the marrow cavities filled with, very cellular fibrous tissue in which numerous areas of osteoid tissue and spicules of calcified bone were scattered. No cartilage was noted. Occasional vascular channels were seen, and a moderate number of multinucleated cells were scattered within the fibrous tissue and along the margins of the bone. No evidence of cyst formation was observed (fig. 2).

Operation.—On September 16 exploration of the neck was performed by Dr. George Muller. There was no gross evidence of parathyroid tumor or hyperplasia and no microscopic evidence of parathyroid tissue in a nodular piece of tissue excised from the thyroid gland, which was reported as showing "adenomatous glandular hyperplasia" (Dr. B. L. Crawford).

At the time of writing, after ten months of observation, the clinical and roentgenographic pictures have altered only in that the patient has become increasingly disabled by pain and weakness and there has been some progression of the bone lesions. Efforts have been made to control the pain by subarachnoid injections of alcohol, and chordotomy is contemplated if other measures are unsuccessful.

COMMENT

In the opinion of the roentgenologist, the skeletal lesions presented a rather characteristic picture of osteitis fibrosa cystica dependent on a state of hyperparathyroidism. There were certain points, however, which weighed strongly against the diagnosis. Among the more important of these were (1) the comparatively early age of the patient at the onset of symptoms (11 years), (2) the consistently essentially normal serum calcium and phosphorus concentrations and serum phosphatase activity and (3) the absence of excessive excretion of calcium in the urine during periods of low calcium intake. The phosphorus content of the diet during these periods was perhaps not low enough to render this observation as conclusive as it would otherwise have been, but it certainly was not high enough to prevent the characteristic excessive urinary excretion of calcium associated with hyperparathyroidism. Moreover, whereas it is possible that osseous lesions due to previous hyperparathyroidism may persist during periods of remission of the latter state, during which no metabolic evidence of such hyperparathyroidism may be demonstrable, it seems inconceivable that such lesions can progress for ten months with no associated manifestations of abnormal parathyroid function. This diagnosis having been excluded and the clinical course of the condition and the absence of other significant findings apparently having excluded multiple myeloma and metastatic malignant lesions, it was felt that the condition was probably either polyostotic fibrous dysplasia or an atypical skeletal xanthomatous

process. The latter was ruled out by the results of examination of the biopsy specimen.

The characteristic features of the lesion in this case closely resemble those described by Lichtenstein [1] and by Jaffe.[2] These consist in replacement of the substantia spongiosa and filling of the medullary cavity by fibrous tissue in which sporadic islands of hyaline cartilage and poorly calcified primitive bone develop by metaplasia and in which are distributed small nests of giant cells and occasional vascular channels. The cortex becomes expanded and thinned owing to encroachment on its endosteal surface by the proliferating fibrous tissue. These changes apparently result from perverted development of the bone-forming mesenchyme, and a congenital basis has been suggested. The diagnosis of polyostotic fibrous dysplasia in this case seems justified on the basis of (1) the consistent absence of abnormality of calcium or phosphorus metabolism during a period of progression of the skeletal lesions, (2) the histologic characteristics of the lesion and (3) the failure to detect any abnormality of the parathyroid glands on surgical exploration of the neck. In our opinion, the latter procedure is not justified in such cases.

Dr. H. L. Jaffe assisted in the interpretation of the histologic sections of the biopsy specimen.

[NOTE.—The patient in the case reported was rehospitalized in June 1939 for a brief period of observation. She no longer had pain in the left hip and left lower extremity, and the discomfort in the right hip and right lower extremity had lessened considerably. Despite weight bearing for short periods daily, there had been no increase in her deformities. There was no roentgen evidence of alteration in the osseous lesions, and no new lesions were apparent. The laboratory findings corresponded with those previously recorded.]

BOECK'S SARCOID

AUTOPSY IN A CASE WITH VISCERAL LESIONS

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An extensive literature has appeared on the subject of sarcoid since the cutaneous lesions were described by Hutchinson (1869), Besnier (1889) and Boeck (1899). In the majority of the cases reported only the cutaneous manifestations have appeared. Kuznitzky and Bittorf [1] in 1915 suggested that there is a generalized distribution of the lesions, and Jüngling [2] in 1920 and in 1928 published his observations on the osseous changes. These publications prompted a further interest in the character and distribution of the visceral lesions. A comprehensive review of the subject is to be found in the recent publication of Longcope and Pierson.[3]

Although the disease with generalized lesions has been well studied, only a few autopsies have been reported. Bernstein, Konzelmann and Sidlick [4] in 1929 reported a case of sarcoid with lesions in the skin, epicardium, bronchial mucosa and mucosa of the ileum. Mylius and Schürmann [5] in 1929 presented 2 cases. In the first, in which there was an associated pulmonary tuberculosis, iritis had been observed clinically, together with cutaneous lesions on the cheek, cystic changes of the phalanges, enlargement of the mediastinal lymph nodes and infiltration of the lungs. Autopsy revealed lesions in the skin, lungs, liver, lymph nodes and phalanges. In the second case only lesions in the lungs and peribronchial lymph nodes were described. Lenartowicz

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1. Kuznitzky, E., and Bittorf, A.: Boecksches Sarkoid mit Beteiligung innerer Organe, München. med. Wchnschr. **62**:1349, 1915.

2. Jüngling, O.: Ostitis tuberculosa multiplex cystica (eine eigenartige Form der Knochentuberkulose), Fortschr. a. d. Geb. d. Röntgenstrahlen **27**:375, 1920; Ueber Ostitis tuberculosa multiplex cystoides, zugleich ein Beitrag zur Lehre von den Tuberkuliden des Knoches, Beitr. z. klin. Chir. **143**:401, 1928.

3. Longcope, W. T., and Pierson, J. W.: Boeck's Sarcoid (Sarcoidosis), Bull. Johns Hopkins Hosp. **60**:223, 1937.

4. Bernstein, M.; Konzelmann, F. W., and Sidlick, D. M.: Boeck's Sarcoid: Report of a Case with Visceral Involvement, Arch. Int. Med. **44**:721 (Nov.) 1929.

5. Mylius, K., and Schürmann, P.: Universelle sklerosierende tuberkulöse grosszellige Hyperplasie, eine besondere Form atypischer Tuberkulose, Beitr. z. Klin. d. Tuberk. **73**:166, 1929.

and Rothfeld [6] in the same year described a case of sarcoid with lesions in the brain, lungs, spleen, gastrointestinal tract, lymph nodes and bones.

Schaumann [7] in 1936 reported 4 cases in 3 of which a thorough clinical study had been made; in the fourth diagnosis was made post mortem. Active tuberculosis was associated with the sarcoid lesions in 2 of the cases. In the first case the lesions had regressed after the development of the active pulmonary tuberculosis. In the second case lesions appeared in the skin, lungs, epicardium, liver, spleen, capsule of the kidney, lymphatics, phalanges and marrow of the humerus and radius. In the third case clinical diagnosis was based on the character of the lesions of the skin, the enlargement of the lymph nodes, the osseous changes and the enlargement of the hilar shadows. At autopsy lesions were seen in the lungs, subepithelial connective tissue of the trachea, gastrointestinal tract, liver, spleen, epididymis, prostate, lymph nodes and lumbar vertebrae. In this case the active tuberculous peritonitis which was present was considered merely a complication. The author stated that the rapidity of death did not permit fibrosis of the sarcoid lesions. In the fourth case, in which diagnosis was made at autopsy, the lymph nodes, spleen, pharynx, liver and lungs were involved.

In July 1937 Nickerson [8] published a report of 6 cases of sarcoid with visceral involvement, in all but 1 of which some other disease caused death. In 1 case, that of a middle-aged Negress, death was due to a widespread sarcoid infection, without cutaneous lesions. The clinical diagnosis was atypical tuberculosis of the lungs and lymph nodes and bronchial asthma. The postmortem diagnosis was atypical tuberculosis, but the condition was later considered sarcoid. A few solitary lesions were noted in the myocardium and endocardium in 1 case. Other organs observed to be involved were the lungs, spleen, liver, pancreas, testis, lymph nodes and bone marrow of the femur and vertebrae.

The report of an unusual case in which generalized chronic infectious granulomas involved especially the myocardium is presented. The course was rapid, terminating fatally within eleven weeks of the development of subjective symptoms. Autopsy was performed one hour and a half post mortem. Because of the character and distribution of the lesions and an inability to demonstrate an etiologic agent, the diagnosis of Boeck's sarcoid was made.

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6. Lenartowicz, J., and Rothfeld, J.: Ein Fall von Hautsarkoiden (Darier-Roussy) mit identischen Veränderungen im Gehirm und den inneren Organen, Arch. f. Dermat. u. Syph. **161**:504, 1930.

7. Schaumann, J.: Lymphogranulomatosis Benigna in the Light of Prolonged Clinical Observations and Autopsy Findings, Brit. J. Dermat. **48**:399, 1936.

8. Nickerson, D. A.: Boeck's Sarcoid: Report of Six Cases in Which Autopsies Were Made, Arch. Path. **24**:19 (July) 1937.

REPORT OF A CASE

Clinical History.—W. L. S., a Negro aged 18, was admitted to the Vanderbilt University Hospital on June 21, 1937. His illness had begun insidiously six weeks before admission and had grown progressively worse, even though he had stopped working, in a beer garden, and spent most of his time resting at home. He had been aware first of marked fatigue and dyspnea on exertion. Later he had noticed slight edema of his ankles, orthopnea and a persistent cough, worse at night and productive of mucoid sputum. Even though his appetite had remained good, he had lost weight, although he did not know exactly how much. He had not experienced pain, hemoptysis, night sweats or chills. He had had influenza during the winter of 1936 but stated that he had not had any other illness. He had not been exposed to tuberculosis. His familial history was noncontributory.

Physical Examination.—The temperature was 99.2 F., the pulse rate 142 and the respiratory rate 48. The patient appeared critically ill, with labored respiration in both inspiration and expiration. He was poorly nourished, although well developed. There was slight venous congestion. The pupils were normal. The tonsils were enlarged and cryptic. The heart was enlarged, with the point of maximum impulse in the sixth interspace in the anterior axillary line, and there was a cardiac dulness at this level of 5.5 by 12 cm. A distinct precordial bulge and a strong systolic pulsation over the area of the right ventricle were observed. The cardiac rate was rapid, and the first sound had a loud slapping quality. The second sound at the pulmonic area was accentuated and reduplicated. The blood pressure was 140 mm. of mercury systolic and 110 diastolic. There were an ascending line of dulness and some suppression of breath sounds in the right axilla. Posteriorly in the midline there was little difference on percussion, and the bases were estimated to occupy a relatively normal position. Numerous rales were heard throughout both lungs, more marked in the lower half, and without definite changes in respiratory sound. The margin of the liver was 3 cm. below the right costal margin and was tender on pressure. Slight pitting edema of the lower extremities was present. There was a moderate general glandular enlargement, the nodes being hard, discrete and nontender.

Laboratory Findings.—The urine was amber and acid, with a specific gravity of 1.006 to 1.015, a trace of albumin and no sugar. There were a few white blood cells and an occasional red blood cell. Many hyaline and granular casts were present.

The blood count was 3,367,000 red cells, with hemoglobin 11 Gm., and 5,680 white cells. The supravital differential count was polymorphonuclear neutrophilic leukocytes, 72 per cent; polymorphonuclear basophilic leukocytes, 1 per cent; polymorphonuclear eosinophilic leukocytes, 1 per cent; small lymphocytes, 4.5 per cent; intermediate lymphocytes, 4.5 per cent, and monocytes, 17 per cent. Wassermann and Kahn reactions were strongly positive. The total serum protein was 6.62 Gm. per hundred cubic centimeters. The albumin fraction was 3.61 Gm. and the globulin 3.01 Gm.

The reaction to 0.1 cc. of old tuberculin (1:100) was negative after forty-eight hours.

The roentgenograms showed a thickening of the hilus of each lung, with heavy infiltration radiating from the hilus to the periphery and base. The heart was somewhat enlarged, and considerable exudation on both sides extended upward from the bases.

Subsequent Course.—The course in general was unsatisfactory, although the patient showed slight improvement at times. Evidence of right ventricular failure

became more marked, and cyanosis of the nail beds appeared. The temperature varied between 98.6 and 100 F., but on several occasions reached 101. The electrocardiographic picture changed from that of sinus tachycardia, with arborization block and low voltage, to that of auricular fibrillation, complete heart block and a shifting pacemaker. The patient died on July 22, of progressive myocardial failure.

Autopsy.—Gross Examination: The body was that of a malnourished Negro of 18, with good skeletal development. The cervical, axillary, inguinal and epitrochlear lymph nodes were slightly enlarged, firm, discrete and movable. The pupils were equal and dilated. The neck, chest and abdomen were not remarkable. A small, firm, movable nodule 1 by 1.5 cm. was present on the flexion surface of the left forearm. There was pitting edema of the ankles. The peritoneum was smooth and glistening. There was 250 cc. of clear straw-colored fluid in the peritoneal cavity. The margin of the liver was 3 cm. below the right costal margin. Fibrous adhesions covered a small nodule in the upper portion of the lower lobe of the left lung and attached the visceral and parietal pleurae at this point. Two hundred cubic centimeters of clear fluid was present in each pleural cavity. The pericardium was smooth, thin and glistening. About 60 cc. of clear fluid was present in the pericardial cavity.

The heart was hypertrophied, weighing 450 Gm. All the chambers were dilated. The myocardium was pale and soft. The myocardium of the left ventricle measured 1.7 cm. The muscle bundles were distorted by numerous irregular opaque yellowish areas, which were seen throughout, occupying a considerable portion of the myocardium. Small, discrete, slightly raised gray nodules, about 2 mm. in diameter, were noted just beneath the endocardium. Several small sessile nodules of a similar appearance were present on the contact surface of the aortic leaflet of the mitral valve. One measured 4 by 2 mm. and the others 2 mm. each. There was no associated shortening, rolling or thickening of the cusps. The cusps of the aortic, the pulmonic and the tricuspid valve were not remarkable. The valves measured: aortic, 5.5 cm.; mitral, 9 cm.; pulmonic, 6 cm., and tricuspid, 12 cm. Mural thrombi were attached to the endocardium of both ventricles. The coronary vessels were not unusual. The aorta showed no evidence of syphilis or atherosclerosis.

The lungs were heavy, the right weighing 720 Gm., and the left 600 Gm. A firm nodule, measuring 1.5 by 2.5 cm., at the periphery of the upper portion of the lower lobe of the left lung was covered by torn fibrous adhesions and was clearly differentiated from the surrounding parenchyma. The cut surface had a gray, opaque appearance. A smaller nodule of a similar character, measuring 6 mm., was observed in the posterior portion of the same lobe. A number of barely palpable minute nodules were present on the surface of the right lower lobe. The dependent portions of the lungs were firm, and an abundance of frothy fluid exuded onto the cut surface. The hilar and peribronchial lymph nodes were much enlarged, measuring from 1 to 2.5 cm. They were firm, glistening and light gray.

The gastrointestinal tract was not remarkable. Several small, firm, slightly raised gray nodules, about 1 mm. in diameter, were noted on the surface of the liver. The spleen, pancreas and adrenals were of normal size, shape, appearance and consistency. The kidneys were of normal weight and appeared swollen and congested, and each contained a fairly large infarct.

Microscopic Examination: The lesions were composed of multiple discrete tubercles as well as many confluent groups of tubercles. The center of the

tubercle was composed of endothelial cells, often associated with a giant cell, and about the periphery there existed a scanty zone of lymphocytes. The giant cells were numerous, often situated at the periphery of the tubercles and frequently containing from twenty to thirty rather irregularly distributed nuclei. In one large giant cell in the myocardium fifty nuclei were counted. When the tubercles

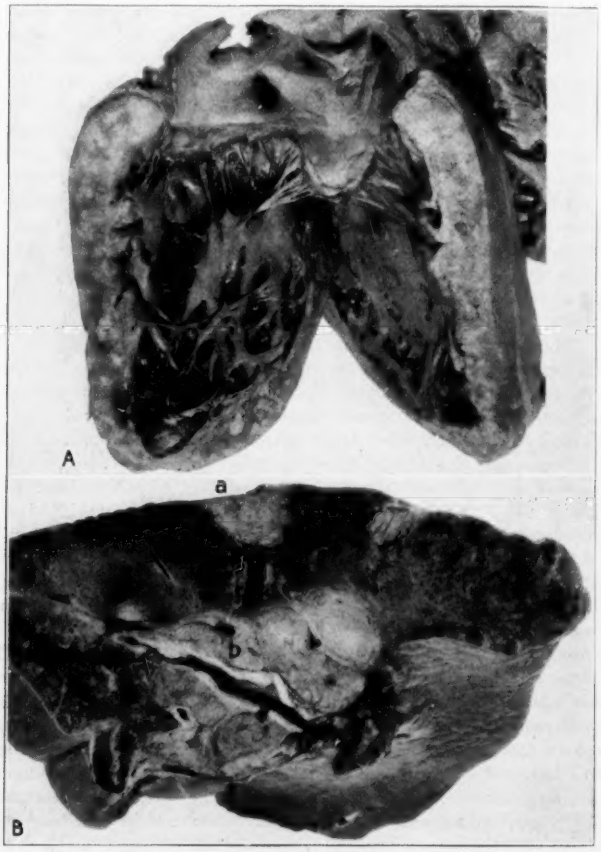

Fig. 1.—*A*, left ventricular myocardium, showing mottling by gray granulomatous foci and a mural thrombus at the apex. *B*, left lung, showing a peripheral nodule (*a*) and enlarged peribronchial nodes (*b*).

became confluent the typical arrangement was lost, and there was an increase in fibrous tissue; this change could be demonstrated extensively with Mallory's collagen stain. A thin zone of collagen was present about the periphery of many of the solitary tubercles. There were a few lymphocytes but no polymorphonuclear leukocytes.

The myocardium had been extensively replaced by chronic inflammatory granulation tissue, in which there was fibrosis but no caseation. The epicardium had been entirely spared and showed no thickening or infiltration. The tubercles had a miliary distribution in the lungs but also coalesced to form nodules, in which

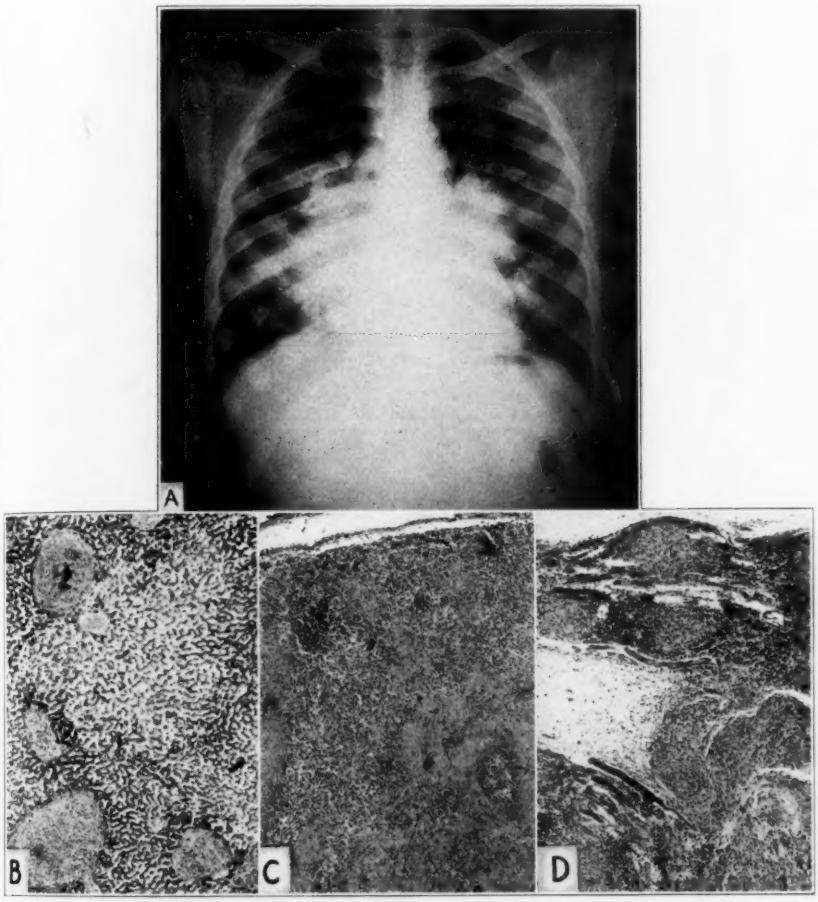

Fig. 2.—*A*, roentgentogram, showing hilar infiltration. *B*, *C* and *D*, photomicrographs showing, respectively, granulomatous foci in the liver, × 32; a bronchial node, granulomatous infiltration with collagenous degeneration and giant cells, × 32; a subcutaneous nodule with granulomatous infiltration of striated muscle, × 32.

there were much fibrosis and slight lymphocytic infiltration but no caseation. The nodules at the periphery of the lower lobe of the left lung had this type of structure. The peribronchial and hilar lymph nodes were extensively involved.

and small areas of caseation could be seen, but they were indeed scant. Many miliary lesions were observed in the liver, which had mainly a periportal arrangement. A few lesions were observed in the spleen, testicle and wall of the alimentary tract.

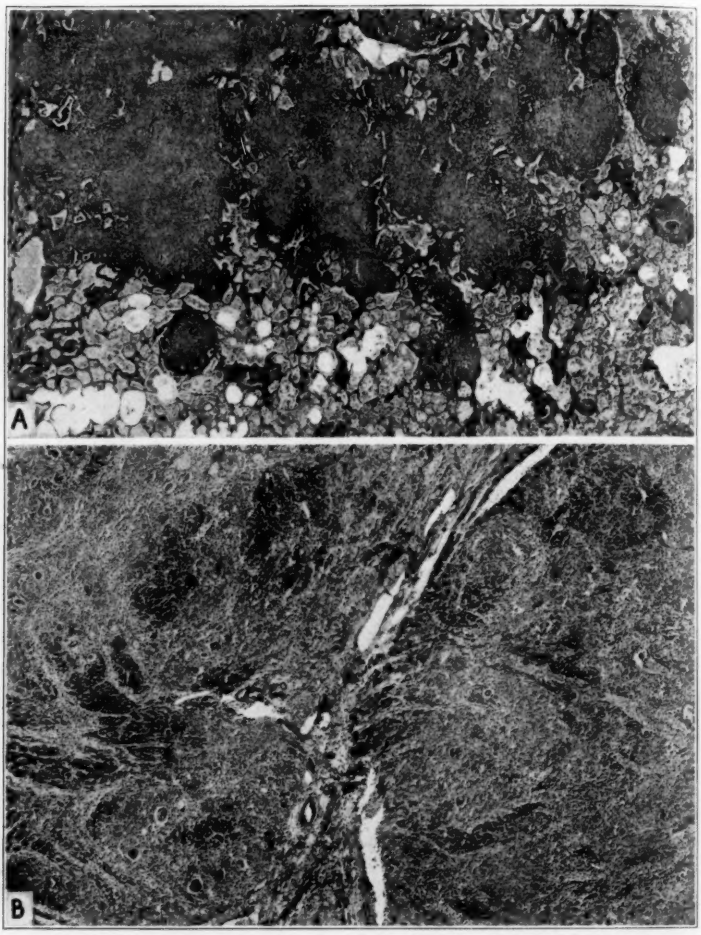

Fig. 3.—*A*, a section of the left lung through the margin of the granulomatous nodule (*a*, fig. 1 *B*), × 15⅝. *B*, a section of the left ventricular myocardium, showing granulomatous infiltration. Numerous giant cells are seen, × 28.

The subcutaneous nodule removed from the left forearm was of particular interest in that it showed the same type of reaction as that described in the heart, lungs and other organs. The nodule extended into the underlying muscle but did not involve the skin.

COMMENT

Clinically, sarcoid is a chronic disease. It persists usually over a number of years, produces only a slight constitutional reaction, seldom responds to treatment, is sometimes recurrent, and most often is associated with a negative tuberculin reaction. The clinical manifestations are characteristic lesions of the skin, enlargement of the superficial lymph nodes and tonsils, widening of the hilar shadows of the lungs, as observed roentgenographically, infiltration of the peripheral fields of the lungs, rhinitis, iridocyclitis, enlargement of the parotid gland, splenomegaly and hepatomegaly. Apparently the tissues of different persons vary markedly in susceptibility. In 1 case the skin may be predominantly involved, in another the lymph nodes and in still another the internal organs. Cutaneous lesions are not present in some cases.

Longcope and Pierson reported a case of Boeck's sarcoid with bilateral iridocyclitis in which also the superficial lymph nodes were enlarged. The lacrimal glands were swollen, and nodules appeared beneath the eyelids and in the parotid glands. Roentgen examination of the chest revealed an enlargement of the hilar shadows and an infiltration of the lungs, particularly on the right side. The authors called attention to the striking resemblance between the condition and that described as uveoparotitis, uveoparotid tuberculosis or uveoparotid fever.

Uveoparotid fever presents the same etiologic problem as sarcoid. It is a chronic condition in which there is mild fever, bilateral uveitis and enlargement of the parotid glands. The disease of the uveal tract usually leads to some impairment of vision, while the parotid glands return to their normal size. Not infrequently there is paralysis of the facial nerve. The tuberculin test is usually negative except in the presence of an active classic tuberculous lesion. Typical cutaneous lesions and osseous changes of sarcoid have not been described as associated with the disease.

Thomson[9] in 1930 reported a case of uveoparotid fever in which an unusual type of diffuse tuberculous infiltration of the myocardium failed to involve the parietal pericardium. The lesions were described as composed of endothelial cells, lymphocytes and giant cells, without caseation and with demonstrable collagen fibers. Miliary lesions were noted in the epicardium, lungs and tracheobronchial and mediastinal lymph nodes. The author was unable to identify the tubercle bacillus in sections but claimed to have observed it after digesting the heart muscle in sodium hydroxide.

9. Thomson, J. G.: An Unusual Case of Diffuse Tuberculous Infiltration of the Myocardium, J. Path. & Bact. **33**:259, 1930.

Garland and Thomson [10] reviewed the literature on uveoparotid fever in 1933 and reported a case in which they found myocardial lesions at autopsy. They considered the condition in their case to be miliary tuberculosis, although they were willing to admit the distribution of the lesions was unusual. They stated that the histologic appearance of the tissue was sufficiently characteristic to warrant a diagnosis of tuberculosis, even though the tubercle bacillus could not be demonstrated. The character of the myocardium was identical with that reported previously by Thomson, and illustrations were included in the publication to stress this point. The absence of caseation was impressive, and collagen fibers could be demonstrated. Lesions were noted in the lungs, liver, kidney, uterus, parotid and submaxillary glands. The peritoneum was markedly involved. There was evidence of an old tuberculous infection of the mesenteric lymph nodes, with caseation and calcification. No lesions were observed in the spleen, on either macroscopic or microscopic examination, which is unusual in cases of miliary tuberculosis.

The classification of my case is based on the character and distribution of the lesions and on my inability to demonstrate an etiologic agent. In typical miliary tuberculosis there is caseation; a primary focus can usually be found, and the tubercle bacilli can be identified in the lesions. The disseminated type of myocardial tuberculosis is rare and represents usually an extension from tuberculous pericarditis. Thomson's case is an exceptional one in this group. In the case I have presented the lesions differed from the classic tuberculous lesions in that they were cellular and contained considerable fibrous tissue and practically no caseation. The myocardium was almost completely replaced by granulation tissue, but the parietal pericardium was not involved. Sections of tissue fixed with solution of formaldehyde and Zenker's solution have been stained for the tubercle bacillus by the Ziehl-Neelsen method, and large pieces of lung, myocardium and lymph nodes have been digested with antiformin (a strongly alkaline solution of sodium hypochlorite) and also with a solution of sodium hydroxide. The centrifuged sediment was then stained for acid-fast bacilli. These attempts to identify the tubercle bacillus have been unsuccessful.

Syphilis has been considered as an etiologic possibility, but it is difficult to imagine the lesions of syphilis having such an unusual distribution and such an extensive myocardial involvement. The duration of syphilis in my case is unknown, but it is known that the patient had never received antisyphilitic therapy. Levaditi stains of autopsy material were prepared on two occasions and negative results obtained in each instance.

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10. Garland, H. G., and Thomson, J. G.: Uveo-Parotid Tuberculosis, Quart. J. Med. **2**:157, 1933.

In Nickerson's case of acute fulminating sarcoid, which was first thought to be an instance atypical tuberculosis, the picture resembled that in my case in many respects. Nickerson stated that a small amount of fibrinoid material in the lesions is consistent with the diagnosis of sarcoid for such fulminating conditions.

The remarkable similarity between the myocardial lesions in the 2 reported cases of uveoparotid fever and those in the present case may indicate some relation between the two conditions. From a clinical aspect this relation has been suggested by Longcope and Pierson, who indicated that uveoparotid fever may be merely a clinical variation of sarcoid.

I do not feel that there is sufficient justification to diagnose tuberculosis in my case, and the evidence presented has led me to believe that the condition can most satisfactorily be considered Boeck's sarcoid.

SUMMARY

A disseminated, chronic, infectious granuloma is reported occurring in a young Negro. The outstanding features are the character and extent of the myocardial involvement. The case is considered one of Boeck's sarcoid, with visceral involvement, without typical cutaneous manifestations and without active classic tuberculosis.

The similarity between the myocardial lesions in this case and those in 2 cases of uveoparotid fever is impressive.

CARDIAC SEQUELAE OF EMBOLISM OF THE PULMONARY ARTERY

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A number of clinical observations have indicated that some of the serious consequences of embolism of the pulmonary artery are due to a deleterious effect on the heart and the coronary circulation. Extensive occlusion of the pulmonary circulation is usually followed by circulatory shock and an associated diminution in the cardiac output. The usual symptom complex of embolism of the pulmonary artery, which is characterized by marked dyspnea, cyanosis, tachypnea, substernal oppression, collapse of the peripheral circulation, apprehension, feeble pulse, profuse perspiration, ashen pallor and low blood pressure, is frequently indistinguishable from the clinical picture observed in coronary occlusion with myocardial infarction. This striking similarity in itself suggests the possibility that the syndrome of embolism of the pulmonary artery may actually result from a diminution of the coronary circulation and associated ischemia of the myocardium. The characteristic electrocardiogram in cases of embolism of the pulmonary artery is frequently identical with or almost indistinguishable from that in cases of infarction of the posterior wall of the left ventricle. The frequency and the nature of these electrocardiographic abnormalities further suggest that the heart is the site of a secondary ischemic alteration. In some cases, sudden death following multiple small emboli in relatively few branches of the pulmonary artery cannot be reasonably ascribed to a significant interference with the pulmonary circulation. A reflex or secondary effect on the coronary circulation and myocardium has consequently been invoked to explain such an occurrence.

PATHOGENESIS OF CARDIAC SEQUELAE AND CAUSE OF DEATH IN EMBOLISM OF THE PULMONARY ARTERY

On the basis of numerous experimental and clinical observations, a number of mechanisms have been adduced to explain the manner in which embolism of the pulmonary artery may affect the circulation and

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cause death. It is extremely difficult to dissociate the individual factors concerned, partly because several of them may act simultaneously and partly because they have an important influence on each other. For purposes of discussion, however, the various factors may be analyzed individually. The main cardiac effects of embolism of the pulmonary artery are due either (A) to mechanical obstruction of the pulmonary artery with strain on the right ventricle or (B) to myocardial ischemia. The latter may result from shock, generalized anoxemia or vagal reflexes from the lungs to the coronary vessels.

A. Obstruction of the Pulmonary Artery.—The mechanical effect of embolism of the pulmonary artery on the circulation may be ascertained from the results obtained by experimental occlusion of this artery or its branches. Various experiments [1] have shown that extreme degrees of obstruction of the pulmonary artery (80 per cent of the lumen or more) are necessary to effect a significant reduction in the systemic blood pressure or to cause death. At the same time, almost complete occlusion of the pulmonary artery induces dilatation of the right ventricle. While more moderate degrees of obstruction of the artery are not followed by dilatation of the right ventricle, they may increase the pressure within that chamber as well as in the pulmonary artery proximal to the obstruction. Thus moderate obstruction of the pulmonary artery may result in evidence of strain on the right ventricle even when there is no visible dilatation.[2]

Clinical observations on human beings indicate that in many instances of embolism of the pulmonary artery there is actually sufficient mechan-

1. (*a*) Welch, W. H.: Zur Pathologie des Lungenödems, Virchows Arch. f. path. Anat. **72**:375, 1878. (*b*) Gerhardt, D.: Experimentelle Beiträge zur Lehre vom Lungenkreislauf und von der mechanischen Wirkung pleuritischer Ergüsse, Ztschr. f. klin. Med. **55**:195, 1904. (*c*) Mann, F. C.: Pulmonary Embolism, J. Exper. Med. **26**:387, 1917. (*d*) Dunn, J. S.: The Effects of Multiple Embolism of the Pulmonary Arterioles, Quart. J. Med. **13**:129, 1920. (*e*) Tigerstedt, R.: Die Physiologie des Kreislaufes, Berlin, W. de Gruyter & Co., 1923. (*f*) Schlaepfer, K.: Ligation of the Pulmonary Artery of One Lung With and Without Resection of the Phrenic Nerve, Arch. Surg. **9**:25 (July) 1924. (*g*) Haggart, G. E., and Walker, A. M.: Physiology of Pulmonary Embolism as Disclosed by Quantitative Occlusion of the Pulmonary Artery, ibid. **6**:764 (May) 1923. (*h*) Gibbon, J. H., Jr.; Hopkinson, M., and Churchill, E. D.: Changes in the Circulation Produced by Gradual Occlusion of the Pulmonary Artery, J. Clin. Investigation **11**:543, 1932. (*i*) Hall, G. E., and Ettinger, G. H.: An Experimental Study of Pulmonary Embolism, Canad. M. A. J. **28**:357, 1933. (*j*) Gibbon, J. H., Jr., and Churchill, E. D.: Physiology of Massive Pulmonary Embolism, Ann. Surg. **104**:811, 1936. (*k*) Jackson, D. E., and Jackson, H. L.: Physiologic Consideration Regarding the Etiology and Nature of Coronary Thrombosis, J. Lab. & Clin. Med. **22**:329, 1937.

2. Fineberg, M. H., and Wiggers, C. J.: Compensation and Failure of the Right Ventricle, Am. Heart J. **11**:255, 1936. Haggart and Walker.[1g]

ical obstruction to produce dilatation of the right side of the heart and significant diminution in cardiac output and systemic blood pressure. In such instances, the embolic mass either blocks the main stem of the pulmonary artery or exists as multiple foci, occluding the lumens of several smaller branches and producing thereby a similar effect. McGinn and White [3] applied the term acute cor pulmonale to a clinical picture which they said was due to the sudden dilatation of the right side of the heart incident to a high degree of obstruction of the pulmonary artery. Of 8 of their patients with embolism of the pulmonary artery, dilatation of the artery was observed in all but 3. The absence of dilatation in the 3 cases was attributed to failure of the right ventricle, shock or the inability of blood to pass beyond the area of obstruction. Churchill [4] also reported observations on patients operated on for embolism of the pulmonary artery in whom the artery was greatly distended, but he occasionally noted that the arteries were collapsed. He explained the latter observation as indicative of failure of the right ventricle. Earlier reports of marked dilatation of the pulmonary artery following embolism may be cited.[5]

Additional evidence of the mechanical effect of embolism of the pulmonary artery on the right side of the heart resides in the following clinical and electrocardiographic observations. White and his associates [6] and Lord [7] noted an accentuation of the second pulmonic sound, which they interpreted as indicating increased pressure in the pulmonary artery. Similarly, they, as well as Litten,[8] reported a thrill and a to and fro murmur over the pulmonic area due to obstruction to the outflow of blood from the right ventricle and dilatation of the pulmonary artery. Gallop rhythm was attributed to the same cause. Mention was made

3. McGinn, S., and White, P. D.: Acute Cor Pulmonale Resulting from Pulmonary Embolism: Its Clinical Recognition, J. A. M. A. **104**:1473 (April 27) 1935.

4. Churchill, E. D.: The Mechanism of Death in Massive Pulmonary Embolism, Surg., Gynec. & Obst. **59**:513, 1934.

5. Farr, C. E., and Spiegel, R.: Pulmonary Infarction and Embolism, Ann. Surg. **89**:481, 1929. Hampton, H. H., and Wharton, L. R.: Venous Thrombosis, Pulmonary Infarction and Embolism Following Gynecological Operations, Bull. Johns Hopkins Hosp. **31**:95, 1920.

6. (*a*) White, P. D., and Brenner, O.: Pathological and Clinical Aspects of the Pulmonary Circulation, New England J. Med. **209**:1261, 1933. (*b*) White, P. D.: The Acute Cor Pulmonale, Ann. Int. Med. **9**:115, 1935. (*c*) McGinn and White.[3]

7. Lord, F. T.: Diseases of the Bronchi, Lungs and Pleura, Philadelphia, Lea & Febiger, 1925, p. 483.

8. Litten, M.: Ueber Verengerungen im Stromgebiet der Lungenarterie, über deren Folgen und die Möglichkeit dieselben während des Lebens zu diagnostizieren, Berl. klin. Wchnschr. **19**:425, 1882.

also of the occurrence of failure of the right side of the heart in cases of embolism of the pulmonary artery as a result of the increased load on the right ventricle. The chief evidence of this was the engorgement of and elevation of pressure in the superficial veins of the neck. Finally, electrocardiograms made in cases both of experimental obstruction of the pulmonary artery [9] and of embolism of the artery in man [10] not infrequently revealed the development of deviation of the electrical axis to the right, a large S_1 and a negative T_3 wave, all of which may be considered evidence of strain on the right ventricle.

B. Myocardial Ischemia.—Sudden obstruction of the pulmonary artery leads to a number of changes which tend to produce myocardial ischemia. The ischemia may be effected by three factors, namely, (1) shock, which is associated with a diminution of the cardiac output and the systemic blood pressure; (2) anoxemia resulting from interference with the pulmonary circulation and diminished oxygenation of the blood, and (3) reflexes by way of the vagus nerve, which may produce a diminution of the caliber of the coronary artery and the blood supply to the myocardium.

1. Shock is a frequent clinical feature in cases of embolism of the pulmonary artery. In such cases there is a marked fall in blood pressure and cardiac output, occasionally to the point where neither the blood pressure nor the pulse can be obtained. These cases correspond to the experiments in which almost the entire pulmonary vascular bed has been occluded. The direct effect of the marked diminution in blood pressure (and consequently in aortic pressure) is to reduce markedly the coronary blood flow. In addition, reduced blood pressure may indirectly cause myocardial anoxemia by interfering with the pulmonary aeration of the blood and by possible reflex influence on the coronary arteries, which will be discussed later.

2. Asphyxia is another common accompaniment of embolism of the pulmonary artery, and not infrequently pronounced degrees of dyspnea

9. (*a*) Otto, H. L.: The Effect of a Sudden Increase in the Intracardiac Pressure upon the Form of the T-Wave of the Electrocardiogram, J. Lab. & Clin. Med. **14**:643, 1929. (*b*) Criep, L. H.: Electrocardiographic Studies of the Effect of Anaphylaxis on the Cardiac Mechanism, Arch. Int. Med. **48**:1098 (Dec.) 1931. (*c*) Anderson, J. P.: Electrocardiographic Findings in Experimental Pulmonary Embolism, abstracted, Am. Heart J. **9**:104, 1933. (*d*) Buchbinder, W. C., and Katz, L. N.: The Electrocardiogram in Acute Experimental Distension of the Right Heart, Am. J. M. Sc. **187**:785, 1934. (*e*) McGinn and White.[3]

10. Langendorf, R., and Pick, A.: EKG-Befunde bei Lungenembolie, Acta med. Scandinav. **90**:289, 1936. Barnes, A. R.: Diagnostic Electrocardiographic Changes Observed Following Acute Pulmonary Embolism, Proc. Staff Meet., Mayo Clin. **11**:11, 1936; Pulmonary Embolism, J. A. M. A. **109**:1347 (Oct. 23) 1937. McGinn and White.[3]

and cyanosis are striking clinical manifestations.[11] Experimentally, Gibbon and Churchill [1j] noted that while the blood pressure did not fall, even with occlusion of 85 per cent of the pulmonary vascular bed, a distinct oxygen unsaturation of the arterial blood occurred when more than 40 per cent of the pulmonary vascular bed had been occluded. The occurrence of varying grades of asphyxia could explain many of the clinical and experimental features of embolism of the pulmonary artery, for these, as well as the electrocardiographic changes observed, are similar to or identical with the manifestations of asphyxia produced by factors other than embolism. Criep [9b] observed that in the rabbit the cardiac changes following acute asphyxia and those following clamping of the pulmonary artery are essentially the same. McGinn and White [3] noted that the electrocardiographic changes following occlusion of the pulmonary artery in cats were similar to those observed in asphyxiated cats by Lewis and Mathison.[12] Furthermore, dilatation of the right chambers of the heart may also be attributed to asphyxia,[3] but it is difficult to dissociate this factor from the possible mechanical effect of vascular obstruction in embolism.

3. The evaluation of the importance of reflexes in controlling the coronary blood flow, as recently emphasized by Wiggers,[13] is beset with many difficulties. Although the presence in the vagus and sympathetic nerves of fibers for vasomotor control to the coronary arteries is well established, there is some difference of opinion as to their exact distribution in these nerves. The weight of opinion [14] appears to indicate that the constrictor fibers to the coronary artery are found in the vagus nerve and the dilator fibers in the sympathetic. Anrep and Segall [14c] found that the coronary flow increased after section of the vagus nerve

11. (*a*) Edens, E.: Die Krankheiten des Herzens und der Gefässe, Berlin, Julius Springer, 1929. (*b*) Averbuck, S. H.: The Differentiation of Acute Coronary Artery Thrombosis from Pulmonary Embolization, Am. J. M. Sc. **187**: 391, 1934. (*c*) Master, A. M.; Jaffe, H. L., and Dack, S.: The Clinical and Electrocardiographic Differentiation of Coronary Thrombosis from Pulmonary Embolism, J. Mt. Sinai Hosp. **3**:288, 1937.

12. Lewis, T., and Mathison, G. C.: Auriculoventricular Heart-Block as a Result of Asphyxia, Heart **2**:47, 1910.

13. Wiggers, C. J.: The Physiology of the Coronary Circulation, in Levy, R. L.: Diseases of the Coronary Arteries and Cardiac Pain, New York, The Macmillan Company, 1936.

14. (*a*) Porter, W. T.: The Vasomotor Nerves of the Heart, Boston M. & S. J. **134**:39, 1896. (*b*) Wiggers, C. J.: The Innervation of the Coronary Vessels, Am. J. Physiol. **24**:391, 1909. (*c*) Anrep, G. V., and Segall, H. N.: The Regulation of the Coronary Circulation, Heart **13**:239, 1926. (*d*) Rein, H.: Die Physiologie der Coronardurchblutung, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **43**:246, 1931. (*e*) Greene, C. W.: The Nerve Control of the Coronary Vessels, Am. J. Physiol. **113**:361, 1935.

while it diminished when the vagus nerve was stimulated with the heart rate controlled. These observations have been corroborated by Rein,[14d] Wiggers [13] and others, who have shown in addition that the vasoconstrictor effect of vagal stimulation on the coronary arteries could be abolished by atropine. Other observations [15] appear to show that the coronary flow is affected by a change in heart rate and blood pressure. It is possible that the effect of vagal stimulation also may be mediated through changes in rate and blood pressure, rather than through a vasoconstrictor effect.

Edens [11a] attributed some importance to vagal influence in embolism of the pulmonary artery and expressed the opinion that cardiac dysfunction and death are due to vagal stimulation rather than to obstruction of the artery. A significant relation of embolism of the pulmonary artery to cardiac function via reflex effect is suggested by certain experimental studies. Direct or reflex stimulation of the endings of the vagus nerve in the lungs or pleura of animals has been shown [16] to result in a decrease in heart rate and blood pressure. Strueff [16c] and Villaret and his co-workers [17] demonstrated that a more significant reflex effect on the heart resulted from small rather than from large emboli of the pulmonary arteries. The latter authors expressed the belief, further, that such reflex effects from stimulation of the terminals of the vagus nerve in the pulmonary arterioles are responsible for sudden death from embolism when there is relatively little obstruction of the pulmonary vascular bed.

Recently Scherf and Schönbrunner [18] attempted to demonstrate the importance of vagal reflexes in dogs by producing embolization of the pulmonary artery without significant obstruction of the pulmonary circulation. Despite removal of the obstructive factor, significant electrocardiographic changes such as are seen in embolism of the pulmonary artery in man were observed in 2 of 10 dogs. The investigators con-

15. Miller, G. H.; Smith, F. M., and Graber, V. C.: The Influence of Changes in the Cardiac Rate and Irregular Action of the Heart on the Coronary Circulation, Am. Heart J. **2**:479, 1927.

16. (*a*) Brodie, T. G., and Russel, A. E.: On Reflex Cardiac Inhibition, J. Physiol. **26**:92, 1900-1901. (*b*) Capps, J. A., and Lewis, D.: Observations upon Certain Blood-Pressure Lowering Reflexes That Arise from Irritation of the Inflamed Pleura, Am. J. M. Sc. **134**:868, 1907. (*c*) Strueff, N.: Zur Frage der bakteriellen Lungenembolie, Virchows Arch. f. path. Anat. **198**:211, 1909.

17. Villaret, M.; Justin-Besançon, L., and Bardin, P.: Physio-pathologie des accidents mortels consécutifs aux embolies pulmonaires, Bull. et mém. Soc. méd. d. hôp. de Paris **52**:936, 1936; Recherches sur la prévention expérimentale des accidents consécutifs aux embolies pulmonaires, ibid. **52**:941, 1936.

18. Scherf, D., and Schönbrunner, E.: (*a*) Ueber Herzebefunde bei Lungenembolien, Ztschr. f. klin. Med. **128**:455, 1935; (*b*) Ueber der pulmocoronaren Reflex bie Lungenembolien, Klin. Wchnschr. **16**:340, 1937.

cluded that these changes had resulted from diminution in the coronary flow produced reflexly by reaction of constrictor fibers in the vagus nerve.

From the foregoing evidence, it seems that vasomotor reflexes may play a significant role in the effect of embolism of the pulmonary artery on coronary flow and cardiac action. Direct evidence of the importance of these reflexes in this condition in man is lacking. Their possible effect is confused by the many simultaneous changes which are induced. Thus, even if one accepts the belief that embolism of the pulmonary artery diminishes the coronary flow by vagal stimulation, the concomitant fall in blood pressure and increase in cardiac rate, as well as the reduction in cardiac output and anoxemia, would tend to modify the effect. Furthermore, the reflex stimulus, if present, would not only affect the coronary flow but would also induce a cardioinhibitory action on the heart, with slowing of the heart rate, delay in conduction and possibly even cardiac standstill.

Most observers have failed to note any organic myocardial alterations which might be anticipated as a result of the obstructive, anoxemic and reflex factors discussed. In many of the reports of cases of embolism of the pulmonary artery in which there were postmortem examinations a distinct statement is made that the coronary arteries were patent and that the myocardium showed no significant abnormality which could be ascribed to the embolism. Recently Kroetz and his co-workers [19] reported that the hearts of 12 patients who had died of embolism of the pulmonary artery showed no fresh, ischemic necrosis of the myocardium, except when thrombotic arterial occlusion was associated. In the absence of detailed protocols and descriptions, especially as to the location and extent of the emboli and the duration of life after embolization, we cannot comment on these observations. The statement that abnormal electrocardiographic signs were not demonstrable after repeated embolization of the pulmonary artery in dogs is contrary to the experience of other investigators.[9]

On the other hand, we have been able to find 2 reports in the literature in which mention is made of myocardial changes following obstruction of the pulmonary artery. Boswell and Palmer [20] observed a case of progressive thrombosis of the pulmonary artery in which subendocardial myocardial degeneration and fragmentation were noted in the

19. (*a*) Eckardt, in discussion on Thaddea, S.: Ueber Elektrokardiogrammveränderungen im Nebennierencoma und ihre Beeinflussung durch das Nebennierenrindenhormon, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **48**:354, 1936. (*b*) Kroetz, C.: Das Herz bei akuten Störungen der Lungendurchblutung und der Lungenbeatmung, abstracted, Klin. Wchnschr. **17**:366, 1938.

20. Boswell, C. H., and Palmer, H. D.: Progressive Thrombosis of the Pulmonary Artery, Arch. Int. Med. **47**:799 (May) 1931.

absence of coronary occlusion. Hamburger and Saphir [21] described an instance (their case 4) of embolism of the pulmonary artery in which a myocardial infarct was associated with coronary sclerosis, but without acute coronary occlusion.

MATERIAL AND METHODS

In a study of the hearts in 42 cases of embolism of the pulmonary artery we observed acute ischemic myocardial damage in 8 (table). Since systematic and diligent search failed to reveal recent coronary occlusion in any of these, we believe the myocardial damage may be related to embolism of the pulmonary artery. In 2 of the hearts there were minute but grossly visible focal areas of necrosis. In the remaining hearts with recent myocardial damage the abnormalities were discovered only after a detailed histologic study.

The hearts which revealed recent myocardial changes and some of those which did not were studied in the fresh state as well as after fixation. On the other hand, many of the hearts in which no such abnormalities were observed at the time of autopsy either were available only as fixed specimens or were not obtainable for reexamination. When the hearts were not available for examination the data were based on the routine protocol descriptions and on restudy of the routine slides which had been saved. In the other instances the specimen was studied in the following manner:

All the major branches of the coronary arteries were systematically investigated. Transverse sections were made throughout the course of each branch at intervals of 2 to 3 mm. Any suspicious site was sectioned in greater detail and studied histologically. Whenever possible, the following branches were cut: the left anterior descending artery and its primary and secondary rami; the left circumflex artery and its branches to the anterior wall of the left ventricle, to the obtuse margin of the heart and to the posterior wall of the left ventricle; the main right coronary artery; the right circumflex artery and its branches to the posterior interventricular sulcus and to the posterior wall of the left ventricle, and the branches of the right coronary artery to the anterior and posterior walls of the right ventricle and to the acute margin of the heart. The branches to the auricles were also examined but were frequently of minute caliber or could not be followed. In addition to searching for occlusion of the coronary arteries, we noted the degree of sclerosis and narrowing of these vessels and their ostiums and graded the changes as 1 to 4 plus according to severity.

The various portions of the myocardium were examined systematically for gross abnormalities; notes were made of the appearance of the anterior and posterior walls of the various cardiac chambers, of the left and right sides of the interventricular septum and of the papillary muscles. Then histologic sections were made from each of these regions, particularly from those areas which we suspected on gross examination to be abnormal. Finally, the pericardium, the endocardium and the valves were observed for abnormalities and the weight of the heart and the size of the cardiac chambers noted. The clinical history

21. Hamburger, W. W., and Saphir, O.: Pulmonary Embolism Complicating and Simulating Coronary Thrombosis, M. Clin. North America **16**:383, 1932.

Anatomic Data on Eight Cases of Recurrent Pulmonary Embolism with Cardiac Damage

Case No.	Age, Yr.	Weight of Heart, Gm.	Cardiac Dilatation*		Coronary Arteries		Anterior Wall of Left Ventricle	Posterior Wall of Left Ventricle	Interventricular Septum	Anterior Wall of Right Ventricle	Posterior Wall of Right Ventricle	Auricles	Cause of Death	Associated Lesions
			Right	Left	Sclerosis	Narrowing								
1	54	430	A + V 0	+ 0	0 to +	0	Foci of necrosis; myodegeneration; fatty change ++	Foci of necrosis with polymorphonuclears; young, edematous connective tissue	Fatty change	Focal myodegeneration; fatty change	Same as anterior wall plus focal necrosis	Tinctorial changes	Embolus of pulmonary artery	Thrombosis of common iliac, femoral and hypogastric veins; edema of lower extremities; essential hypertension; hypertrophy of all cardiac chambers
2	44	350	A ++ V ++	0 +	++	++ to +++	Focal necrosis; mesenchymal cell proliferation; patchy fibrosis; subendocardial hemorrhage	Focal necrosis; hemorrhage; vacuolar changes; fatty changes; patchy fibrosis	Focal fine necrosis; polymorphonuclears; interstitial hemorrhage	Degenerative changes; polymorphonuclears	Degenerative changes; polymorphonuclears	0	Embolus of pulmonary artery	Hypertrophy of left ventricle; acute congestion of liver and spleen
3	58	465	A +++ V ++	0	+	0	Subendocardial tinctorial changes	Patchy young connective tissue	Focal necrosis; fatty change; vacuolation; polymorphonuclears; edematous young connective tissue	Patchy young connective tissue	0	0	Embolus of pulmonary artery	Two carcinomas of large intestine, with metastases to mesentery, omentum and liver; pulmonary arteriosclerosis; hydrothorax (200 cc.) on left
4	75	400	A 0 V +	0	+++	+++ to ++++	Focal necrosis and hemorrhage; polymorphonuclears	Fatty change +; fibrosis	Focal necrosis with polymorphonuclears; interstitial hemorrhage; fatty change	Focal hemorrhage (fine)	0	Fine fibrosis; fatty change +++	Embolus of pulmonary artery; cardiac failure	Hypertrophy of heart; myofibrosis with aneurysmal dilatation of left ventricle; nephrosclerosis; bilateral hydrothorax

5	65	380	A ++ V 0	+	++	++	Focal hemorrhage; subendocardial myodegeneration	Myodegeneration; focal lymphocytes	Young connective tissue focus	Minute focal necrosis with polymorphonuclears and lymphocytes	Patchy myodegeneration	0	Embolus of pulmonary artery	Hypertrophy of both ventricles; status 11 days after ligation of vas and 45 min. after transurethral prostatectomy; pulmonary infarct in lower lobe of left lung
6	55	300	A + V +	+ +	+	0	Myodegeneration (slight); patchy fibrosis	Focal interstitial hemorrhage; myodegeneration with polymorphonuclears and lymphocytes, mainly subendocardial	Minute focal areas of necrosis with polymorphonuclears; subendocardial	0	0	Myodegeneration	Embolus of pulmonary artery; pulmonary edema	Eleven days after mastectomy, acute congestion of liver; chronic cholecystitis
7	64	560	A ++ V +++	++ +++	+++	+++ to ++++	Foci of hemorrhage; fibrosis	Minute focal necrosis; myodegeneration; interstitial focus of polymorphonuclears	0	0	0	Fibrosis	Embolus of pulmonary artery; cardiac failure	Old infarct of anterior wall of left ventricle; mural thrombosis of right auricular appendage and both ventricles
8	70	450	A ++ V ++	++ ++	++ ++	++ ++	Myodegeneration with polymorphonuclears	Foci of interstitial hemorrhage; fibrosis	0	Tinctorial change	0	Fibrosis	Cardiac failure	Hypertrophy and dilatation of heart; thrombosis of left auricular appendage; pulmonary infarct; thrombosis of iliac veins

* A = auricle; V = ventricle.

and the extracardiac pathologic changes were studied in order to evaluate the role of various possible factors in the production of myocardial disease and coronary insufficiency. In the selection of our cases those were eliminated from study in which there was evidence of infection because of the possible effect of such infection on the myocardium.

REPORT OF CASES

The following are protocols of 4 of the 8 cases in which acute ischemic myocardial changes were observed without concomitant recent coronary occlusions. For the sake of brevity, 4 of the cases, in which there were definite but less marked myocardial alterations, are omitted from detailed consideration.

CASE 1.—A woman aged 54 had been observed for four years because of hypertensive heart disease. During this period she suffered from precordial pressure, dyspnea on exertion, attacks of nocturnal dyspnea, headaches, vertigo and weakness. The systolic blood pressure had ranged between 200 and 250 and the diastolic pressure between 100 and 130 mm. of mercury. Electrocardiograms (fig. 1 *A*) had revealed left axis deviation, high voltage of the QRS complex, depression of the RS-T intervals in leads I and II and inversion of T_1, T_2 and T_4. These changes were ascribed to enlargement of the left ventricle. Three weeks before admission to the hospital she suffered right hemiplegia. Four days before admission nausea, vomiting, weakness and increasing dyspnea had developed.

Examination on admission revealed a pale, drowsy woman. Her heart was moderately enlarged to the left, and her heart sounds were of poor quality. A loud, harsh systolic murmur and a systolic thrill over the entire precordium were now present. The blood pressure had fallen to 130 mm. of mercury systolic and 80 mm. diastolic. An electrocardiogram (fig. 1 *B*) showed partial heart block, with frequent dropped beats. The RT transitions were now markedly depressed in leads I, II and IV. The following day the heart block disappeared, but the marked tachycardia and the deviations of the RT transition persisted (fig. 1 *C*).

On the day after admission the patient's blood pressure dropped to 88 mm. of mercury systolic and 70 mm. diastolic; the temperature rose to 101.6 F., and the leukocyte count to 20,000 per cubic millimeter. She became more dyspneic and cyanotic; the respiratory rate rose to 50, and numerous moist rales appeared in both lungs. Cheyne-Stokes respiration developed, and the patient died three days after admission.

The postmortem diagnosis was thrombosis of the common, external and internal iliac veins, with repeated embolization of the pulmonary arteries; infarction of the lower lobes of the lungs; hypertrophy of the heart, with dilatation of the auricles; slight coronary arteriosclerosis without narrowing; focal myocardial infarction, and chronic cholecystitis and cholelithiasis, with focal fatty necrosis of the pancreas.

The heart appeared moderately enlarged and weighed 430 Gm. The right auricle was dilated and its musculature somewhat thickened. The wall of the right ventricle was slightly hypertrophied, but there was no dilatation of the right ventricular chamber. Immediately proximal to the pulmonary conus was pronounced bulging of the interventricular septum into the cavity of the right ventricle. The pulmonic ring was not widened. A coiled, tubular, gray-red

thrombus, with dull and granular surface, filled the main stem of the pulmonary artery. It extended from the level of the pulmonic ring into the left pulmonary artery and its branches, but only slightly into the right pulmonary stem. The embolus in the left pulmonary artery was seen to be adherent to the intima of that artery and its smaller divisions. The wall of the left auricle was slightly, and that of the left ventricle markedly, hypertrophied. The subendocardial portion of the myocardium, especially in the interventricular septum and the papillary muscles, but also along the anterior and the septal aspect of the left ventricle, showed yellowish brown and moist red mottling. Similar changes of less degree were observed in the right ventricular subendocardial myocardium. Fine gray perivascular streaks were scattered in the deeper portions of the left ventricular

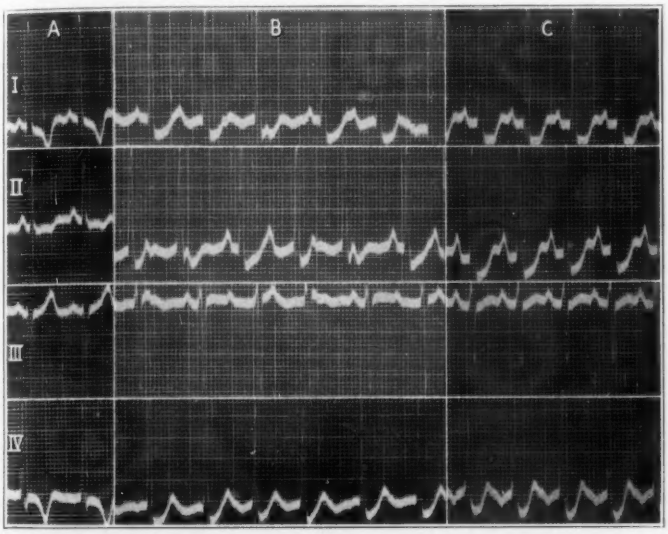

Fig. 1 (case 1).—Electrocardiograms. *A*, two years before admission; regular sinus rhythm, rate 110; marked preponderance of the left ventricle and high voltage of the QRS complex. The T wave is deeply inverted in leads I and IV and diphasic in lead II. The record is characteristic of enlargement of the left ventricle as seen in cases of long-standing hypertension. *B*, one day after admission; incomplete auriculoventricular dissociation, with frequent dropped beats; auricular rate 150; ventricular rate 100 to 140. The RS-T transition is markedly depressed in leads I, II and IV. The T wave has become diphasic in leads I and II, low in lead III and upright in lead IV. *C*, two days after admission; regular sinus tachycardia, rate 140, with normal auriculoventricular conduction. The depression of the RS-T transition in leads I, II and IV is more marked; there is also a slight depression in lead III.

myocardium. The coronary ostiums were normal. The coronary arteries revealed only slight intimal thickening, without encroachment on the lumen and without any occlusions.

Histologic examination of multiple sections of the left ventricle (figs. 2 and 3) revealed widely scattered myofibrils which had undergone necrosis, fatty change and vacuolation, with reactive foci of polymorphonuclear leukocytes, small round cells and fibroblasts. There were also foci of edematous connective tissue. Sections of the wall of the right ventricle revealed, in addition to tinctorial changes, such as smudgy eosinophilic staining of the fibrils with loss of striation, necrosis of the myofibrils, fatty change, scattered interstitial polymorphonuclear

Fig. 2 (case 1).—Section of the left ventricle (× 150), showing severe myodegeneration and cellular infiltration.

leukocytes and proliferation of young, interstitial fibroblasts. Sections of the auricular myocardium showed peculiar tinctorial changes indicating degeneration of the myofibrils.

Comment.—This patient, who was known for four years to have severe hypertension and electrocardiographic changes which occur in hypertension, had few or no evidences of heart failure three weeks

before admission, when she suffered hemiplegia. It is highly probable that the venous thrombosis developed during the three weeks of rest in bed which followed this cerebral accident. The embolism of the pulmonary artery probably occurred in the week before admission, during which time severe dyspnea, weakness, vomiting, a fall in blood pressure and irregular cardiac rhythm were present. The development

Fig. 3 (case 1).—Section of the left ventricle (× 400), showing focal necrosis of the myocardium, with reactive infiltration of polymorphonuclear leukocytes.

of a loud, harsh systolic murmur and a systolic thrill and the practical absence of a second sound were undoubtedly due to pulmonary stenosis caused by the extension of the embolus in the pulmonary artery through the pulmonic ring with occlusion of the pulmonary orifice.[22] The

22. White and others (footnote 6). Lord.[7] Litten.[8]

marked depression of the RS-T transitions and the development of heart block were the consequences of the embolism. The occasional occurrence of heart block in coronary thrombosis and in experimentally induced anoxemia [23] suggests that in this case also it was due to myocardial changes resulting from embolism of the pulmonary arteries. Of interest are the observations of auriculoventricular dissociation by Frommel [24] and McGinn and White [3] in experimental occlusion of the pulmonary vessels. Histologic studies revealed that the emboli in the present case were in various stages of organization, which indicated that there had been multiple embolization at different times during the past week. The recent distinct myocardial changes, seen both grossly and microscopically, could not be ascribed to organic coronary disease since this was minimal and there was neither narrowing nor occlusion of the coronary vessels.

Case 2.—A man aged 44 had suffered from mild dyspnea on exertion for one year and increasing dyspnea and orthopnea for two or three months. He had also had substernal burning on walking against the wind. Three weeks before admission, while he was walking on the street, sudden severe pain developed in the right scapular region, which was aggravated by respiration and cough. He became dyspneic, so that he had to go to bed, but the symptoms all subsided in one hour. The next day the symptoms recurred for two and one-half hours and were followed by a cough and bloody expectoration.

On examination the patient was found to be dyspneic and orthopneic. There was dulness to flatness at the base of the right lung posteriorly, where diminished breath sounds and fine moist rales were heard. The heart was enlarged to the right and left; the heart sounds were of good quality, and there was a short rough systolic murmur at the base of the heart. The second aortic sound was louder than the second pulmonic. The blood pressure was 140 mm. of mercury systolic and 80 mm. diastolic. The liver was not palpable. There was edema of both feet. The venous pressure was 4.5 cm. of water, the saccharin circulation time twenty-two seconds, the vital capacity 1,100 cc., the temperature 101 F. and the white blood cell count 15,600 per cubic millimeter.

The clinical diagnosis on admission was coronary sclerosis, congestive heart failure and pulmonary infarction. Fluid developed at the bases of both lungs. The venous pressure remained the same, and the circulation time became normal. A teleroentgenogram of the chest showed slight enlargement of the left ventricle, elevation of the diaphragm, thickened pleurae, a small pleural effusion on the left and infiltration of the lower lobe of the left lung. An electrocardiogram (fig. 4) revealed left axis deviation, a large Q_3, a large S_1 and deep inversion of T_3. The QRS complex was M shaped in lead II. Ten days after admission precordial oppression and air hunger, restlessness and cyanosis suddenly developed. The patient's heart sounds became feeble, and he died fifteen minutes later.

23. Resnik, W. H.: Observations on the Effect of Anoxemia on the Heart: I. Auriculo-Ventricular Conduction, J. Clin. Investigation **2**:93, 1925. Lewis and Mathison.[12]

24. Frommel, E.: Les troubles du rhythme cardiaque au cours de l'embolie pulmonaire, J. de physiol. et de path. gén. **26**:247, 1928.

The postmortem diagnosis was multiple emboli of the pulmonary artery and its branches; multiple infarcts of the lower lobe of the right lung; sclerosis of the coronary arteries with narrowing, especially of the right circumflex artery; myofibrosis of the posterior wall of the left ventricle; hypertrophy of the left ventricle, and nephrosclerosis. The site of origin of the embolus could not be ascertained, because the incision at autopsy was limited.

The heart weighed 350 Gm. The right auricle was slightly dilated and contained within its lumen two free, grayish red, granular, friable masses. The right ventricular chamber was moderately dilated and contained coiled embolic masses

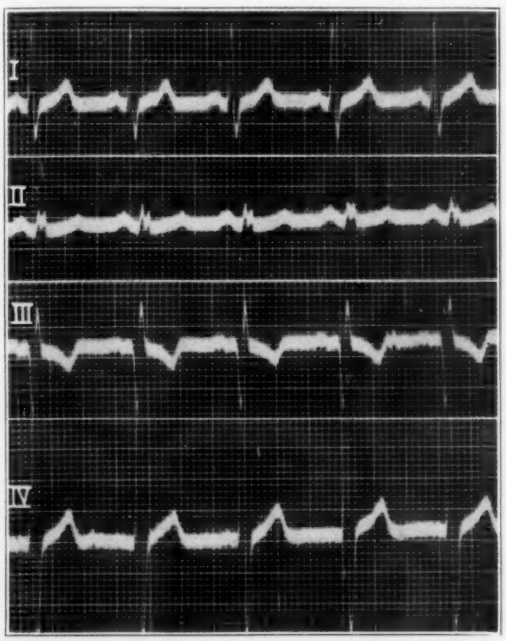

Fig. 4 (case 2).—Electrocardiogram made on admission; regular sinus rhythm, rate 90, deviation of the axis to the left. There are a deep S_1 and a deep Q_3. The QRS complex is M shaped in lead II. T_3 is inverted. The record is suggestive of either posterior myocardial infarction or embolism of the pulmonary artery.

similar to those in the right auricle. The lumen of the left main trunk of the pulmonary artery contained a granular, bloodlike, cylindric body, which extended into the right main branch and the branch to the lower lobe of the right lung and occluded the latter. The embolus in the main right pulmonary artery had become adherent to the intimal surface. The myocardium of the posterior wall of the left ventricle showed an extensive, stellate, gray-white, firm, fibrous zone. The coronary ostiums were patent. There was widespread sclerosis of the coronary arteries, especially of the right, with moderate narrowing of the lumens.

Histologic examination of various portions of the left ventricle revealed focal areas of myomalacia, with subendocardial hemorrhage, vacuolar degeneration of the myofibrils, scattered proliferation of mesenchymal cells and occasional wide zones of interstitial polymorphonuclear leukocytes. There was also evidence of patchy fibrosis and a moderate degree of fatty change. Sections through the right ventricle showed evidence of myodegeneration, with an occasional polymorphonuclear leukocytic reaction.

Comment.—This patient had apparently suffered from mild anginal symptoms and recent slight failure of the left side of the heart probably due to an organized myocardial infarct. The swelling of the right ankle three weeks before admission may have indicated the occurrence of thrombophlebitis of the right leg, from which subsequent embolization of the pulmonary artery occurred. Undoubtedly the first embolism took place three days before admission, when the patient had the sharp thoracic pain and dyspnea, while the hemoptysis on the day before admission must be considered indicative of pulmonary infarction. There had been mild symptoms of failure of the left side of the heart for three months, but they had disappeared shortly after admission, at which time the circulation time and venous pressure were normal. During the ten subsequent days, before final embolism caused death, there was evidence neither of cardiac failure nor of shock. The electrocardiogram made on admission showed the changes which are accepted as common in cases of embolism of the pulmonary artery but which might more probably have been due to an organized infarct of the posterior wall of the left ventricle. Post mortem examination revealed acute myocardial changes which could not be accounted for by any recent coronary occlusion.

Case 3.—A housewife aged 58 had suffered from bleeding hemorrhoids for many years. Four and a half months before admission pain developed in the left upper quadrant of the abdomen, associated with slight fever. Five days before admission there were symptoms of intestinal obstruction. Except for abdominal distention and the presence of external and internal hemorrhoids, the physical examination showed no abnormality. The size and sounds of the heart were normal. The blood pressure was 140 mm. of mercury systolic and 80 mm. diastolic.

With the patient under spinal anesthesia, a cecostomy was performed for carcinoma of the descending colon. The patient's convalescence was uneventful until the eighth day after operation, when she suddenly went into coma and became pale and slightly cyanotic. Her respirations were stertorous and rapid. She died ten minutes later.

The postmortem diagnosis was massive recurrent embolism of the pulmonary artery; carcinomas of the descending and sigmoid colon, with hepatic and mesenteric metastases; localized fibrinous peritonitis at the site of cecostomy; hypertrophy of the heart; pulmonary congestion and edema; hydrothorax on the left side; dilatation of the right auricle and ventricle, and coronary sclerosis without narrowing. Permission for necropsy did not allow a peripheral search for the origin of the thrombus.

The heart weighed 465 Gm. The right auricle was considerably dilated. The right ventricle was moderately dilated, and its trabeculae carneae were considerably flattened. Within the right ventricular chamber and extending into the pulmonary artery were several portions of an inelastic, grayish red blood clot, approximately 7 cm. in length and 1.5 cm. in width. This clot extended also into the medium-sized ramifications of the pulmonary artery. The coronary ostiums and vessels were widely patent throughout. Their walls showed only a moderate number of flat, intimal arteriosclerotic plaques.

Histologic examination of the septum revealed scattered foci of fatty change and glycogen. There were several localized areas of necrosis, with early cellular response of polymorphonuclear leukocytes and lymphocytes. These foci were situated chiefly in the subendocardial zones. There were also patches of edematous and young (cellular) connective tissue. Within the right ventricle were slightly patchy cellular zones of connective tissue.

Comment.—In this case the previous history was not suggestive of cardiac disease. Evidence of massive embolism of the pulmonary artery first appeared on the eighth day after an operation, possibly from a thrombus in the veins of the lower extremities. The appearance of the lungs suggested repeated embolization. Death occurred within ten minutes after the onset of collapse. Acute microscopic cardiac damage was observed, without any noteworthy concomitant coronary disease.

CASE 4.—An actress aged 75, who had had rheumatic fever in childhood and had known that she had valvular heart disease for at least twenty years, had been free from symptoms until four years before admission, when dyspnea and precordial pain developed on exertion. Two weeks before admission, while rehearsing in a play, she became markedly dyspneic when at rest and orthopneic. Six days before admission she had a sharp attack of dyspnea and substernal pressure, which radiated to the back. These symptoms increased until she was admitted to the hospital.

Examination revealed an orthopneic and dyspneic woman in severe shock, with marked pallor of the skin and cyanosis of the extremities, especially of the nail beds. The respiratory rate was 36 and the pulse rate 124, per minute. The skin was cold and moist, and the veins of the neck were full, but those of the extremities were collapsed. The heart was enlarged to the left, and the heart sounds were of poor quality. The second aortic sound was louder than the second pulmonic. The blood pressure was 95 mm. of mercury systolic and 60 mm. diastolic. Respiratory sounds were diminished, with dulness and rales at the bases of both lungs, especially on the left. Slight edema of the ankles and sacral region was noted. Pulsation of the dorsalis pedis arteries was absent.

The clinical diagnosis was multiple occlusions of the coronary arteries, with recent embolization of the pulmonary artery. Despite various therapeutic measures, the patient died several hours after admission.

The postmortem diagnosis was multiple recent pulmonary infarcts, with multiple emboli in the arteries of all lobes of the lungs; coronary arteriosclerosis, with extreme narrowing of the right circumflex artery; myocardial fibrosis, especially of the posterior wall, with aneurysmal dilatation; mural thrombus of the left ventricle, and bilateral hydrothorax.

The heart weighed 400 Gm. The right ventricle was slightly hypertrophied and its chamber somewhat dilated. The interventricular septum bulged considerably into

the lumen of the right ventricle. The endocardium over the posterior wall of the left auricle showed slight, irregular wrinkling. There was diffuse thickening of the mitral leaflets and of their associated chordae tendineae. An aneurysmal dilatation of the left ventricle was observed near its apex. There were several grayish red masses adherent to the left ventricular endocardium and embedded among the trabeculae carneae. Section of the myocardium in this region showed diffuse grayish white streaking and fine yellowish tigering. The coronary ostiums were patent. There was moderate thickening of the coronary arteries, with scattered zones of severe narrowing but no evidence of recent occlusion. Within the branch of the pulmonary artery to the upper lobe of the right lung was a friable gray-white embolus, approximately 10 cm. in length, partially occluding the lumen. Section of the lobes of the lung disclosed many grayish red embolic masses projecting from the mouths of the small branches of the pulmonary artery.

Histologic examination of sections of the anterior and septal portions of the left ventricle showed focal zones of necrosis with polymorphonuclear leukocytic reaction, severe vacuolar degeneration of the muscle and distinct tinctorial changes. There were also widespread foci of interstitial hemorrhage. The right ventricle showed focal hemorrhage and fibrosis, with only moderate fat. The posterior wall of the left ventricle showed only slight fatty change.

Comment.—This patient, with rheumatic heart disease, had suffered from symptoms of cardiac failure and precordial pain for four years. These can be attributed to the old myocardial infarct and ventricular aneurysm observed at postmortem examination. Embolism of the pulmonary artery began one or two weeks before admission and was probably secondary to peripheral venous thrombosis. While the emboli did not occlude the main pulmonary artery, as in the previous cases, there were numerous emboli in the smaller branches, so that much of the pulmonary bed was obstructed. Although there was definite disease of the coronary arteries with marked narrowing, there were no recent occlusions to explain the recent myocardial necrosis.

COMMENT

In the 4 cases presented, microscopic study of the myocardium revealed significant acute damage of the type usually seen in cases of recent coronary occlusion. In 4 other cases, of a similar but distinctly less pronounced condition, more localized myocardial alterations were observed. In 2 cases (1 and 4) recent myocardial damage was suspected on macroscopic examination because of a yellowish brown mottling of the subendocardial myocardium, associated with fine gray perivascular streaking. Other gross changes of the myocardium could be ascribed to fibrosis due to previous coronary occlusion, such as occurred in 2 instances. The microscopic alterations varied in severity and extent from tinctorial changes, loss of striation, fatty change and vacuolation of fibers to focal areas of necrosis, with reactive foci of polymorphonuclear leukocytes, round cells and, finally, fibroblasts. These changes were more predominant in the subendocardial region. In 3 instances

these acute alterations affected both ventricles as well as the interventricular septum. The left ventricle, however, was much more frequently, and usually more extensively, affected. We have not sufficient data to state whether the posterior or the anterior wall of the left ventricle was more severely damaged. Generally the ischemic changes were seen in both walls. In addition, the intensity of the damage was difficult to evaluate because of the association of fibrotic zones in some of the cases.

An attempt was made to determine the factors which led to the development of acute myocardial damage in some cases of embolism of the pulmonary artery and not in others. In one group of 29 cases which were studied there was evidence of recurrent embolization, and death occurred days or weeks after the first embolism. In a second group of 13 cases there was a single embolus in the pulmonary artery with sudden death within a few hours or minutes. All cases of acute myocardial damage fell into the first group. This indicates that the duration of life after embolization is an important factor in the development of myocardial change. Apparently such damage did not develop unless days or weeks elapsed after the initial embolus.

The cases in which acute myocardial damage occurred and those in which it did not were compared with regard to the severity of coronary arteriosclerosis and narrowing. In the latter group the coronary arteries showed relatively little or no sclerosis and no narrowing, except in 2 cases, in which it was slight. On the other hand, in the group comprising cases of embolism of the pulmonary artery with acute myocardial damage the coronary arteries usually showed widespread sclerosis and narrowing. In 5 of the 8 cases of acute myocardial damage there was moderate to extreme narrowing of the lumen of one or more major branches of the coronary arteries. In 2 of these there were severe sclerotic narrowing of the coronary arteries and old myocardial infarction. However, in 3 of the cases of acute myocardial damage there was no significant narrowing of the coronary vessels. Distinct areas of grossly visible myomalacia occurred in the cases in which the most intense narrowing of the coronary arteries was observed. In 2 instances of grossly visible change, however, the lumens of the coronary arteries were normal in caliber, but the heart was distinctly hypertrophied. From these data, it appears that acute myocardial damage occurs most freqently in association with narrowing of the coronary arteries but that such damage may also occur, although less frequently, when the coronary arteries show no significant anatomic alteration, provided the heart is hypertrophied.

The weights of the hearts which showed acute myocardial damage were compared with the weights of those which did not. While there were distinct variations in each group, with few exceptions the hearts

with acute myocardial damage were considerably hypertrophied, while those without such damage were relatively normal. The average weight of the heart in the first group was 390 Gm. and that in the second group was 357 Gm. These averages are partly misleading, because in the first group the heart in 1 or 2 cases weighed less than 350 Gm., but belonged to a cachectic person and might have been regarded as hypertrophied if the cardiac weight had been considered in terms of low body weight. On the other hand, the weight of the heart in 1 case in the second group was recorded as 580 Gm., but the heart itself was not available for study, and only a few routine sections of the myocardium could be examined histologically. With these possible exceptions, it appeared that acute myocardial changes occur much more readily in hypertrophied hearts than in those of normal size. In summary, then, acute alterations following recurrent embolism of the pulmonary artery were favored by three factors: (1) duration of life from several hours to one or more weeks after the initial embolus, (2) preexisting coronary arteriosclerosis with narrowing and (3) hypertrophy of the heart.

The chronologic relation between embolism of the pulmonary artery and the acute myocardial damage cannot be determined with certainty. Any conclusion that the embolism played a role in the production of the myocardial changes would necessarily presuppose proof that the embolism occurred before the development of the myocardial change. That this relation actually existed in the cases described can be inferred only indirectly. Consideration of the clinical history indicates that the first pulmonary accident generally occurred a week or more prior to the death of the patient. It is probable, at least, that in some of the cases the first embolism occurred three or more weeks before death, because there was a rapid fall in blood pressure at that time which could not be explained by any factor other than the embolism. While the age of the myocardial lesion cannot be definitely determined, the changes in some of the areas give the impression of being recent, and probably of only a few days' duration. The chief reason for believing that the embolism preceded the acute myocardial changes is the absence of any other factor which could reasonably account for the production of such myocardial injury. In 2 cases in which the condition occurred there was evidence of an old coronary occlusion (marked arterial narrowing) with a corresponding old, healed infarct. But neither in these nor in any of the other cases in which myocardial damage was noted was there any evidence, on detailed examination, of a recent coronary obstruction such as might be expected to produce the acute myocardial changes which we observed.

Finally, one must consider the possible role of cardiac failure in causing these myocardial changes. There was a significant degree of heart failure in 3 of the 8 cases presented. In each of these there was severe narrowing of the coronary arteries with myofibrosis, which prob-

ably precipitated the failure. Whether myocardial failure with its attendant disturbances in circulatory dynamics is capable of producing acute myocardial damage is uncertain. In these 3 cases it would be difficult to understand why failure of several months' or years' duration should suddenly precipitate acute myocardial damage. The only reason this possibility is entertained is the observation in other studies which we have made on coronary insufficiency, that, under special circumstances, cardiac failure may play a role in the production or exaggeration of acute myocardial damage. In the present series, however, the absence of cardiac failure in 5 of the 8 cases in which the condition was seen clearly indicates that some other factor must be invoked to explain the recent damage to the muscle.

The theoretic cause of death and basis for the occurrence of cardiac sequelae in embolism of the pulmonary artery have been discussed. In the cases which we studied, the embolism caused a sufficient degree of obstruction of the pulmonary vascular bed to be a factor in the production of profound shock and of death. In some of the cases the main pulmonary artery was practically completely occluded, while in others so many of the major branches were obstructed that an equivalent amount of interference with the pulmonary circulation must have existed.

Despite the extent of obstruction of the pulmonary circulation, significant dilatation of the right side of the heart was not invariably present. A marked degree of dilatation was observed in only 2 of the cases of recurrent embolism of the pulmonary artery and in only 2 of the 13 cases in which death followed a single embolus. Moderate or slight dilatation of the right ventricle was encountered in many of the cases, but it should be emphasized that the evaluation of such lesser degrees of dilatation at postmortem examination is fraught with difficulties and is therefore uncertain. Furthermore, except for the 2 instances of severe dilatation of the right ventricle after a single fatal embolus of the pulmonary artery, other factors, such as failure of the left side of the heart, may have been responsible. The infrequency of dilatation of the right ventricle may be explained in some cases by the rapidity with which death ensued and in others by the intense shock following extreme obstruction of the pulmonary circulation and diminution of blood volume returning from the periphery to the right ventricle. In 1 of our cases a loud systolic murmur and a systolic thrill gave evidence of obstruction of the pulmonary artery—signs already pointed out by Litten.[8] Special reference to the second pulmonic sound was not found in the records of these patients. In 1 case it was observed that there was an elevation of pressure in the cervical veins without a similar rise in the peripheral veins. This may not necessarily be interpreted as indicating failure of the right side of the heart, because in the

presence of shock, with its peripheral vasoconstriction, there may have been a redistribution of blood from the periphery to the cerebral vessels, with relative increase in venous return from the latter and diminution from the former.[25]

The explanation for the anatomic myocardial changes observed in our cases appears to lie in the development of ischemia of the myocardium. Of the theoretic causative factors discussed earlier, neither pulmonary-coronary vagal reflexes nor generalized anoxemia can be invoked. That constriction induced by vagal stimulation could occur in severely sclerotic coronary arteries seems anatomically unlikely. Shock with a concomitant drop in systemic, and therefore in aortic, blood pressure was probably the dominant factor in the production of myocardial ischemia and of the acute myocardial injuries which we have described. Marked degrees of shock and diminution in blood pressure were present in all the cases in which anatomic examination disclosed acute myocardial damage. Furthermore, electrocardiographic changes when present always followed the onset of clinical shock with diminution in blood pressure.

The explanation for the occurrence of acute myocardial damage in some cases and not in others has already been attempted. Apparently the myocardial ischemia induced by diminished aortic pressure was inadequate unless other favorable elements were present. Thus we believe that when the myocardium was already suffering from previous coronary disease with narrowing or old occlusion sufficient to cause relative ischemia, or when the heart was large with an abnormally great demand for blood, or particularly when with these combined factors recurrent embolism of the pulmonary artery reduced the blood pressure over a sufficiently long period, the degree of ischemia became adequate actually to produce its morphologic expression. Then, even in the absence of a recent coronary occlusion, coronary insufficiency was precipitated by the fall in aortic pressure adequate to induce acute myocardial damage, which in some instances was similar in severity to that observed in cases of actual coronary occlusion.[26] Support for this concept is found in our observation, which is the subject of another report,[27] of similar acute myocardial damage in the absence of acute coronary occlusion in conditions other than embolism of the pulmonary artery, in which shock coexisted with coronary disease. In cases of

25. Fishberg, A. M.: Redistribution of Blood in Heart Failure, J. Clin. Investigation **17**:510, 1938.

26. Büchner, F.; Weber, A., and Haager, B.: Koronarinfarkt und Koronarinsufficienz in vergleichender elektrokardiographischer und morphologischer Untersuchung, Leipzig, Georg Thieme, 1935.

27. Friedberg, C. K., and Horn, H.: Acute Myocardial Infarction Not Due to Coronary Artery Occlusion, J. A. M. A. **112**:1675 (April 29) 1939.

severe shock lasting several days such organic damage may be produced even though there is no significant coronary disease, as seen in our first case.

In view of the anatomic changes which we have described, it appears that the typical electrocardiographic alterations observed in cases of embolism of the pulmonary artery, which so closely simulate those of myocardial infarction, could be explained on the basis of myocardial ischemia. However, electrocardiographic changes typical of embolism of the pulmonary artery, such as depression of the RS-T transition in lead I and elevation in lead III, inversion of T_2 and T_3 and a large Q_3, also were observed in some of the cases in which no anatomic changes were seen in the myocardium. But even in these cases it appeared fair to assume that myocardial ischemia was present, even though it was not of sufficient severity or duration to result in organic alteration of the heart muscle. That temporary coronary insufficiency can induce such functional changes in the myocardium is shown by the acute transient electrocardiographic changes observed in patients during an attack of angina pectoris due to disease of the coronary arteries. These patients may return to their previous functional status, with complete and rapid regression of the objective and subjective phenomena, after removal of the factor which has produced coronary insufficiency.

Some of the electrocardiographic changes found in cases of embolism of the pulmonary artery, such as the tendency to right axis deviation and the development of a large S_1 wave, probably represent strain on the right ventricle. The absence of dilatation of the right ventricle, as seen post mortem or even at operation, does not preclude the existence of increased tension on the pulmonary artery and the right ventricle.[2] That strain on the right ventricle and engorgement of the inferior vena cava do exist was indicated by the report of Keschner and Klemperer,[28] who showed that hepatic edema is approximately as frequent in cases of embolism of the pulmonary artery as in those of prolonged cardiac failure. Furthermore, the development of these evidences of strain on the right ventricle depends in part on whether the relative size of the cardiac chambers was previously normal or whether there was hypertrophy of the left ventricle associated with hypertension and hypertensive heart disease.

Love and his co-workers [29] concluded, as a result of their studies on experimental embolism of the pulmonary artery in dogs, that the elec-

28. Keschner, H. W., and Klemperer, P.: Frequency and Significance of Hepatic Edema, Arch. Path. **22**:583 (Nov.) 1936.

29. Love, W. S., Jr.; Brugler, G. W., and Winslow, N.: Electrocardiographic Studies in Clinical and Experimental Pulmonary Embolization, Ann. Int. Med. **11**:2109, 1938.

trocardiographic changes observed were due entirely to dilatation of the right ventricle. These findings cannot be applied directly to embolism in man, not only because of the difference in species but because the experiments were of brief duration and the hearts and coronary vessels were normal. In our cases of acute cardiac damage the embolism was recurrent, with several days at least elapsing before death, and the hearts were generally hypertrophied and the coronary arteries narrowed.

The absence or presence of electrocardiographic changes in cases of embolism of the pulmonary artery and their variations in appearance might be explained by variations in the degree of myocardial ischemia and of strain on the right ventricle. The former would depend on the severity and duration of shock, the absence or presence of previous severe coronary disease and the vascular demands of the muscle mass, and the latter, on the absence or presence of previous preponderance of the left ventricle and the cross-sectional area of arterial obstruction.

It is not clear why the electrocardiographic pattern of embolism of the pulmonary artery resembles that of posterior rather than that of anterior myocardial infarction. The only experimental evidence which bears on this point is that of Buchbinder and Katz,[9d] who observed that after compression of the pulmonary artery the heart revealed epicardial and intramuscular hemorrhages in the basal portion of the ventricles. In our anatomic observations there did not appear to be a preponderance of myocardial damage either at the base of the heart or on the posterior wall. Neither could we observe any evidence that the blood supply of the right coronary artery was more impaired than that of the left. However, the marked rise in intraventricular pressure that must have been present within the right ventricle might have increased the resistance to flow in the right coronary artery [30] sufficiently to affect disproportionately those portions of the heart, particularly the posterior wall, which are supplied by that vessel.

SUMMARY AND CONCLUSIONS

A group of 42 cases of embolism of the pulmonary artery has been studied, in 8 of which recent structural changes in the myocardium ordinarily resulting from acute myocardial ischemia were revealed.

The factors necessary for the production of such myocardial changes are discussed. These are shock, asphyxia and exaggerated vagal reflexes resulting from obstruction of the pulmonary arteries. These factors, alone or in association, lead to insufficiency of the coronary circulation.

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30. Gregg, D. E.: Phasic Blood Flow and Its Determinants in the Right Coronary Artery, Am. J. Physiol. **119**:580, 1937.

Morphologic evidence of coronary insufficiency in cases of embolism of the pulmonary artery is more likely to occur if there are recurrent embolization, narrowing of the coronary arteries, cardiac hypertrophy and adequate duration of life after embolism.

Anatomic changes in the myocardium in persons with embolism of the pulmonary artery may be considered the end result of the myocardial ischemia which accounts for the characteristic electrocardiographic changes.

The resemblance of electrocardiographic changes in cases of embolism of the pulmonary artery to those in cases of myocardial infarction of the posterior wall may be explained by the diminished flow through the right coronary artery resulting from increased tension in the right ventricle.

CALCIUM AND DIGITALIS SYNERGISM

THE TOXICITY OF CALCIUM SALTS INJECTED INTRAVENOUSLY INTO DIGITALIZED ANIMALS

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Certain similarities in the action of the glucosides of the digitalis group and of calcium on the heart have led to the hypothesis that they may be related in their action.[1] There is no general agreement as to the character of this relation. Some investigators have maintained that

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1. (*a*) Billigheimer, E.: Ueber Wirkung und Zusammenhänge von Calcium und Digitalis, Klin. Wchnschr. **8**:724-726 (April 16) 1929. (*b*) Bower, J. O., and Mengle, H. A. K.: The Additive Effect of Calcium and Digitalis: A Warning, with a Report of Two Deaths, J. A. M. A. **106**:1151-1153 (April 4) 1936. (*c*) Fischer, H.: Beitrag zur Frage des Synergismus zwischen Digitalis- und Calciumwirkung, Arch. f. exper. Path. u. Pharmakol. **130**:194-241, 1928. (*d*) Gold, H., and Edwards, D. J.: The Effects of Ouabain on the Heart in the Presence of Hypercalcemia, Am. Heart J. **3**:45-50 (Oct.) 1927. (*e*) Gold, H., and Kwit, N.: Digitalis and Calcium Synergism, Science **86**:330-331 (Oct. 8) 1937. (*f*) Goldberg, S. J.: The Use of Calcium Gluconate as a Circulation Time Test, Am. J. M. Sc. **192**:36-41 (July) 1936. (*g*) Golden, J. S., and Brams, W. A.: Mechanism of the Toxic Effects from the Combined Use of Calcium and Digitalis, Ann. Int. Med. **11**:1084-1088 (Jan.) 1938. (*h*) Lieberman, A. L.: Studies on Calcium: VI. Some Inter-Relationships of the Cardiac Activities of Calcium Gluconate and Scillaren-B, J. Pharmacol. & Exper. Therap. **47**:183-192 (Feb.) 1933. (*i*) Loewi, O.: Ueber den Zusammenhang zwischen Digitalis- und Kalziumwirkung, Arch. f. exper. Path. u. Pharmakol. **82**:131-158 (Dec. 20) 1917. (*j*) Mandelstamm, M.: Ueber den Zusammenhang zwischen Digitalis- und Calciumwirkung, Ztschr. f. d. ges. exper. Med. **51**:633-651, 1926. (*k*) McGuigan, R. A., and Higgins, J. A.: The Influence of Calcium Salts on Digitalis Action, J. Lab. & Clin. Med. **23**:839-844 (May) 1938. (*l*) Wolffe, J. B., and Bellet, S.: Cessation of Attacks of Auricular Paroxysmal Tachycardia by the Use of Calcium, Ann. Int. Med. **4**:795-803 (Jan.) 1931.

their effects are partially or completely additive;[2] others, that they are truly synergistic;[3] in other words, the effects resulting when they are given together exceed the effects to be expected from the sum of their individual actions. The term potentiation is at times used in a sense equivalent to that of synergism.

The experiments presented here are concerned with the effects on the previously digitalized animal of calcium salts injected intravenously. This particular problem has evident special importance in clinical medicine.

PROCEDURE AND RESULTS

Effects of Calcium Alone.—The effects on the heart of calcium salts injected intravenously into dogs have been reported in detail elsewhere.[4] Serial electrocardiograms were taken during the course of continuous intravenous infusion of an isotonic solution of calcium chloride, and the sequence of changes up to the time of the death of the dogs was observed. By determining the concentration of calcium in samples of blood serum taken at intervals during the infusion, it was possible by interpolation to establish the concentration of calcium associated with each change in the electrocardiographic sequence.

A phase of inhibition appeared first, manifested by slowing and all degrees of auriculoventricular block. This occurred at concentrations of calcium of 15 to 40 mg. per hundred cubic centimeters. At slightly higher levels, 30 to 65 mg. of calcium per hundred cubic centimeters, a phase of enhanced automaticity developed, associated with extrasystoles and tachycardia and culminating in ventricular fibrillation and death in half of the experiments. In the animals in which ventricular fibrillation did not develop, this period of enhanced automaticity was replaced by a second slowing phase, terminating in cardiac arrest at concentrations of calcium in the serum of 79 to 190 mg. per hundred cubic centimeters.

The mode of death could not be correlated with the rate of injection. Death by arrest occurred at higher levels of calcium in the serum and so required larger doses of calcium than death by fibrillation, but this is merely an expression of the fact that the animals dying by arrest survived the period of increased automaticity. It gives no clue to the reasons for the death of some and the survival of others beyond this period. Death occurred in some cases after the administration of as little as one tenth of the dose of calcium required to kill others. The

2. Lieberman.[1h] Mandelstamm.[1j] McGuigan and Higgins.[1k]

3. Billigheimer.[1a] Fischer.[1c] Gold and Edwards.[1d] Gold and Kwit.[1e] Golden and Brams.[1g]

4. Hoff, H. E.; Smith, P. K., and Winkler, A. W.: Electrocardiographic Changes and Concentration of Calcium in Serum Following Intravenous Injection of Calcium Chloride, Am. J. Physiol. **125**:162-171, 1939.

great variations in the levels of calcium in the serum at which death occurred and in the doses required to kill make it difficult to speak with any accuracy of a lethal dose of calcium.

Effects of Digitalis Alone.—Digitalis is now usually standardized by the intravenous injection of the drug in divided doses every few minutes until the animal succumbs.[5] The acute fatal dose as determined by this divided dose method, although it yields consistent results, is necessarily higher than that determined by any single dose method, as the portions injected in the last intervals will not have had time to exert their full effects before death occurs. The most recent determinations of the acute fatal dose of digitalis in dogs has been made by McGuigan[6] and by McGuigan and Higgins,[1k] the average amount according to their experiments being 1.0 to 1.2 cc. of the tincture per kilogram of body weight.

In the experiments reported in this paper a tincture was freshly prepared from standardized leaves and adjusted to the U. S. P. standard. In order to determine its potency, the diluted tincture was injected intravenously into 6 normal dogs, the dose being 0.6 cc. per kilogram, or one-half the expected acute fatal dose as determined by the divided dose method. Three of the animals died one to six hours later, with the typical contracted heart of digitalis poisoning. The other 3 survived. This demonstrates the approximate identity of half the acute fatal dose as determined by McGuigan and the 50 per cent lethal dose as usually determined for most drugs. The latter is defined as that dose which will produce death in half the animals studied without consideration of time of death. These experiments serve to define pharmacologically the dose of digitalis used in our later combined experiments and indicate the expected toxic result if digitalis were to be given alone without calcium.

Effects of Calcium on the Digitalized Heart.—Twelve dogs under morphine analgesia were given 0.6 cc. of well diluted tincture of digitalis per kilogram of body weight. One hour later, electrocardiograms of all the animals showed a typical digitalis effect on the heart, with changes in the T wave and ectopic arrhythmias. Calcium chloride was then administered exactly as in the case of nondigitalized dogs, during which samples of blood were taken periodically and serial electrocardiograms recorded from lead II. The results obtained are summarized in table 1. Chart 1 is a schematic representation of the electrocardiographic changes.

5. Sollmann, T.: A Manual of Pharmacology, Philadelphia, W. B. Saunders Company, 1936.

6. McGuigan, R. A.: Pressor and Other Effects of Antipyretics on Digitalis Action, Proc. Soc. Exper. Biol. & Med. **38**:314-315 (April) 1938.

The effect of the injection of calcium was indistinguishable from its influence on the normal heart. The phase of inhibition was first to appear, and it effectively suppressed the ectopic beats and arrhythmias of the digitalized heart. After this the phase of increased automaticity appeared, during which 3 of the 12 animals died suddenly of ventricular fibrillation. The 9 other animals survived the period of hyperexcitability of the heart and succumbed eventually to cardiac arrest. The hearts of

TABLE 1.—*Protocols of Experiments*

Experiment No.	Weight of Dog, Kg.	Injections: Cc. 0.205 Molar Solution of Calcium Chloride	Injections: Cc. per Kg. per Min.	Specimen of Serum: Time, Min.	Specimen of Serum: Calcium, Mg. per 100 Cc.	Mode of Death
1	7.5	28	0.35	....	10.2	
				10.5	41.4	Arrest
2	4.7	50	0.38	....	11.0	
				20.5	49.4	
				27.0	71.4	Arrest
3	10.0	130	0.48	....	11.2	
				10.0	30.2	
				27.5	77.6	Arrest
4	6.6	92	0.49	....	11.0	
				16.0	51.4	
				27.0	72.4	Arrest
5	7.1	185	0.50	....	11.4	
				11.0	31.4	
				37.0	51.4	
				53.0	122.4	Arrest
6	5.4	47	0.92	....	11.0	
				9.5	69.4	Arrest
7	6.0	25	1.05	....	10.0	
				4.0	33.4	Fibrillation
8	7.2	76	1.10	....	10.8	
				9.5	111.6	Arrest
9	7.8	20	1.50	....	11.0	
				17.0	47.2	Fibrillation
10	4.8	73	1.70	....	11.2	
				9.0	135.2	Arrest
11	7.9	185	1.95	....	10.0	
				12.0	59.2	Arrest
12	4.7	11	3.50	....	11.0	
				0.7	46.6	Fibrillation

these animals were not in contraction typical of digitalis poisoning, nor were they completely dilated, as were those of the animals that died of fibrillation.

There are certain ranges of concentration of calcium in the serum at which the principal electrocardiographic changes occur. In chart 2 the concentrations at which these changes appear are compared with the concentrations at which similar changes appeared in the electrocardiograms of the control animal. The data for only 10 of the 20 normal dogs used in the earlier study are included here for purposes of comparison, since the remainder received preliminary medication other than

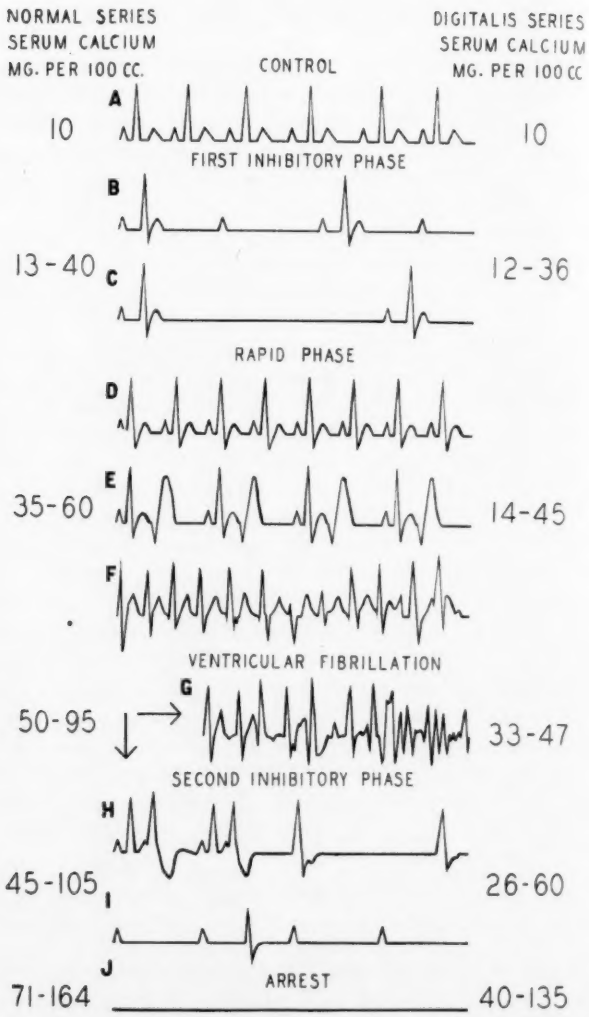

Chart 1.—A diagram indicating the electrocardiographic changes produced by the injection of calcium chloride into normal and digitalized dogs. The curves are copies of actual electrocardiograms obtained in a number of experiments. *A*, control dog, showing slight sinus arrhythmia. *B* and *C*, two typical records showing slowing, auriculoventricular delay and block. Changes in the ST interval and the T wave are shown. *D*, *E* and *F* represent the most common events of the rapid phase, namely, a rapid normal rhythm, bigeminus and ventricular tachycardia from various foci. At this point two alternative events occur: The tachycardia may terminate in ventricular fibrillation and death (*G*), or the second slowing phase may intervene (*H*), and the animal will succumb to cardiac arrest (*J*). At the sides are given the extreme ranges of serum calcium values at which the events occurred.

morphine alone. The figures derived from the digitalized animals overlap extensively those from the control series, although on the whole they tend to be somewhat lower.

A comparison of the average total amounts of calcium given in each of the two series indicates that there is in this respect no significant difference between them. Such a comparison is, however, open to the

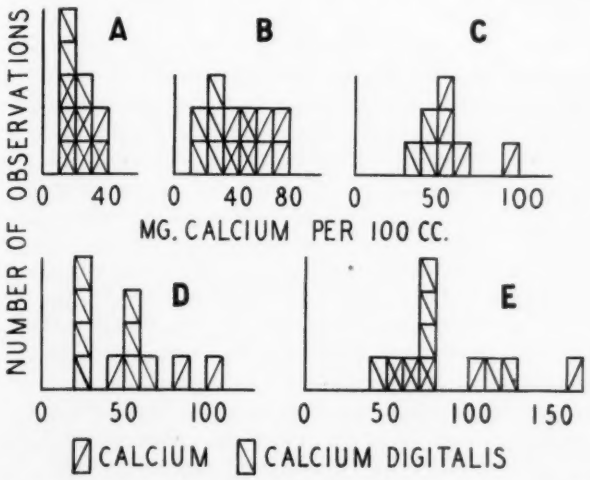

Chart 2.—The concentrations of calcium in the serum of normal and digitalized dogs at which typical electrocardiographic changes occur. *A*, the first slowing phase; *B*, the first rapid phase; *C*, ventricular fibrillation; *D*, the second slowing phase, and *E*, arrest.

TABLE 2.—*Concentration of Calcium in Serum at Death*

In Normal Animals, Mg. per 100 Cc.	In Digitalized Animals, Mg. per 100 Cc.	In Normal Animals, Mg. per 100 Cc.	In Digitalized Animals, Mg. per 100 Cc.	In Normal Animals, Mg. per 100 Cc.	In Digitalized Animals, Mg. per 100 Cc.
106	40	53	120	46	59
71	71	57	60	124	33
164*	78	60	112		47
51	70	96	135		47
Mean				83	73
Probable error of mean				8.3	6.4
Significance ratio 0.9†					

* This value differs by more than two standard deviations from the mean and may be discarded. If this is done, the new values are: mean, 74; probable error 6.3, and significance ratio 0.1.

† The significance ratio is equal to $\frac{D}{PE_d}$; D equals the difference between the two means, PE equals the probable error and PE_d equals $\sqrt{(PE \text{ of one mean})^2 + (PE \text{ of the other mean})^2}$. Differences of means are usually considered statistically significant if the significance ratio is greater than 3.0.

objection that the solution was given at varying rates, thus introducing the amount excreted as an undetermined variable. Accordingly the statistical analysis of these figures is not given. A sounder basis of comparison is used in table 2, in which are summarized the concentrations of calcium in the serum in the normal and in the digitalized dogs. The means and the small significance ratios indicate that the concentrations were not significantly lower in the digitalized animals.

COMMENT

There is no evidence from the results presented here that an unusually small dose of calcium will be fatal to the digitalized animal, nor is there evidence that digitalis potentiates calcium by rendering the heart more susceptible to ventricular fibrillation, since 9 animals died in arrest and only 3 from fibrillation.

Evidence for a completely additive action is also lacking. Neither the total quantity of calcium given nor the concentration of calcium in the serum at death was as low as 50 per cent of comparable values for the nondigitalized dogs. The slight reduction in the lethal quantities and concentrations of calcium found here may be indicative of a partially additive effect. Since some partial addition of effects of any two cardiac poisons may reasonably be expected, it is unnecessary to interpret these partially additive results in terms of a specific relation.

It is probable that findings of potentiation reported in the literature are due to two factors: (1) sudden death from ventricular fibrillation produced by calcium at unusually low levels, which occasionally occurs in normal animals, and (2) the fact that half the acute fatal dose of digitalis may kill within an hour or more approximately half the animals to which it is given. The death of such an animal some time after the administration of calcium may be due to the digitalis alone. This may be the explanation of the death in ventricular fibrillation of certain of the animals studied by Golden and Brams,[1g] who gave 50 to 85 per cent of the acute fatal dose of digalen, and by Bower and Mengle,[1b] who gave comparable doses. The experiments of Gold and Edwards [1d] are not directly comparable, since they gave the calcium before giving ouabain.

A lack of additive effect or of potentiation does not, however, mean that the administration of calcium chloride to digitalized patients or to any patients is an entirely safe procedure. Calcium chloride alone, given intravenously to normal animals, is a toxic drug,[4] its toxicity depending both on the rate of injection and on the total amount given. Its administration to a patient whose failing circulatory system has already occasioned the use of digitalis is probably more dangerous than its administration to other patients, since calcium, like digitalis, has

been shown to produce death by circulatory failure.[6] Our experiments suggest that the danger of injecting calcium into the digitalized patient is simply that of injecting calcium into any patient with cardiac disease and that this in turn probably involves only some intensification of the danger involved in injecting calcium intravenously into a healthy subject. Certainly this danger cannot be great in practice, considering the widespread use of calcium intravenously, often no doubt in the presence of cardiac disease.[7]

Our experiments indicate that whatever danger is involved in the intravenous use of calcium can be minimized by very slow injection of the salts, so that the local concentration in the heart never attains an unsafe level.

SUMMARY

Dilute solution of calcium chloride was administered intravenously to digitalized dogs, and electrocardiograms and samples of blood were taken frequently during the course of the injection.

The electrocardiographic changes were correlated with the concentration of calcium in the serum. They were similar in every way to those of normal animals receiving calcium.

The mode of death of the digitalized animals was by ventricular fibrillation or by arrest without fibrillation, just as in normal animals.

A comparison of the fatal dose and of the concentration of calcium in the serum at death in normal and digitalized dogs indicated that, by the type of experiment described here, the lethal effects of calcium and digitalis are neither synergistic nor even completely additive.

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7. Walters, W., and Bowler, J. P.: Pre-Operative Preparation of Patients with Obstructive Jaundice: An Experimental Study of the Toxicity of Intravenous Calcium Chloride Used in the Preparation of Patients, Surg., Gynec. & Obst. **39:** 200-206 (Aug.) 1924. Luten, D.: The Clinical Use of Digitalis, Springfield, Ill., Charles C. Thomas, Publisher, 1936. Goldberg.[1f]

RELATION OF MYASTHENIA GRAVIS TO HYPERTHYROIDISM

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The neuromuscular syndrome named myasthenia gravis has been recognized since its description by Willis [1] in 1685. Since that time many hypotheses have been presented in the literature, but it must be admitted that as yet the essential cause or causes of myasthenia gravis are unknown. This communication is offered as a record of some empiric data concerned with the relation of the uncommon condition myasthenia gravis to the common syndrome of hyperthyroidism. A case is reported in which the two conditions appeared concurrently and in which the one seemed to inhibit or antagonize the other. Observations on a case of myasthenia gravis in which hyperthyroidism was artificially produced are given, together with a review of the literature.

REPORT OF A CASE

M. B., a woman aged 20, was first seen in June 1936. At that time she stated that she had generally been in excellent health until the middle of April, when she saw single objects doubly. This diplopia lasted only a few days and ceased when the left eyelid began to droop. Shortly after this episode she began to tire easily. She became fatigued readily when chewing and swallowing her food. She consulted an ophthalmologist for the visual disturbance and as a result of his advice had a tonsillectomy performed under general (ether) anesthesia. On recovering from this operation she noticed little change in her symptoms except that her facial expression was unaccustomedly blank and her speech at times thick.

Examination at this time revealed an anxious, tired-looking patient with ptosis of the left eyelid. Her gait and station were normal. The cranial nerves showed the following abnormalities: ptosis of the left lid, palsy of the left external rectus muscle, weakness of both superior rectus muscles, weakness of the right external rectus muscle, blank facial expression and rapid tiring of the tongue on repeated movements. There were no sensory disturbances, and the reflex activities were normal. Weakness of the muscles of the extremities was noticed only on prolonged effort.

At this time (June 1936) an ampule of prostigmine (0.5 mg.) was given intramuscularly as a therapeutic test. Within five minutes of the injection the physical signs and symptoms had all but completely disappeared, and the diagnosis

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1. Willis, cited by Guthrie, L. G.: Myasthenia Gravis in the Seventeenth Century, Lancet **1**:330, 1903.

of myasthenia gravis was made. The patient was referred for admission to the Graduate Hospital for further study.

She was admitted to the Graduate Hospital on July 1, to the service of Dr. J. C. Yaskin, at which time physical examination showed some minor changes in the distribution of the extraocular weaknesses. It was noted that her symptoms were at a minimum in the morning and increased as the day wore on. The thyroid gland was slightly enlarged. The degree of weakness was such as to confine her almost constantly to bed. The pulse rate varied from 75 to 120, and the basal metabolic rate was + 19 per cent. The Wassermann reaction of the blood and of the spinal fluid were negative. The spinal fluid pressure, chemical estimations and cell count were normal. Examination of the blood showed the sugar content to be 93 mg., the urea nitrogen content 10 mg. and the cholesterol content 160 mg. per hundred cubic centimeters. Roentgenograms of the skull were normal, and there was no roentgen evidence of an enlarged thymus or a substernal thyroid gland.

During the patient's stay in the hospital, aminoacetic acid, benzedrine and acetylbetamethyl choline (mecholyl) were given in physiologic doses. It was not until tablets of prostigmine were given orally that definite and unequivocal improvement was seen. This drug was given in doses of 15 mg. three to seven times a day.

The patient continued to lead a fairly normal existence but was dependent on the supply of prostigmine. In February 1937 we prescribed roentgen therapy over the thymic area, but there was no apparent change in the symptoms as measured by the amount of prostigmine necessary. In June 1937, daily injections of 3 cc. of thymus extract (Hanson) were given, with the result that the amount of prostigmine needed to control the symptoms was reduced. In September 1937 a control injection of physiologic solution of sodium chloride was substituted for the thymus extract, and the amount of prostigmine used was about one 15 mg. tablet two or three times a week, which was considerably less than the patient had heretofore required. At the same time it was noted by both the patient and the examiner that the cardiac rate had increased distressingly and that the neck was swollen. The cardiac rate was frequently observed to be above 200. The basal metabolic rate was now + 52 per cent; the cholesterol content of the blood was 178 mg. per hundred cubic centimeters, and the electrocardiogram showed simple tachycardia of sinus origin. In the presence of these symptoms of thyrotoxicosis it was observed that the myasthenic symptoms had all but vanished. No medication of any kind was given at this time. It was decided to treat the delicately balanced antagonism conservatively, and irradiation therapy over the thyroid gland was begun. After two series of such treatments the basal metabolic rate had retreated to + 30 per cent and the cardiac rate was measurable at about 140 to 180. After two months a third series of thyroid irradiation treatment was given, and in another two months the basal metabolic rate was + 19 per cent, the thyroid gland was distinctly smaller and extraocular palsies again became evident. An occasional tablet of prostigmine was then found to be necessary. The pulse rate continued to range between 90 and 130.

COMMENT

It is felt that this case represents a physiologic antagonism between myasthenia gravis on the one hand and hyperthyroidism on the other. At the time of writing the equilibrium established between the two

appears satisfactory from the therapeutic standpoint.[1a] This experience naturally suggested the therapeutic potentiality that artificial hyperthyroidism induced by oral administration of thyroid might be tried in a case of uncomplicated myasthenia gravis. Accordingly, a case of myasthenia gravis of moderate severity was selected, and treatment with thyroid given. Subjectively and objectively the evidences of myasthenia were reduced, while the pulse rate went to 120 and the basal metabolic rate to + 22 per cent (from + 5 per cent). The appearance of irritability, excessive perspiration and palpitation in this case indicated that, although the aforementioned antagonism was again evident, there was little therapeutic justification for the continuance of artificial hyperthyroidism.

The question arises whether there was not originally some etiologic connection between the therapy directed at the thymus gland and the hyperthyroidism which subsequently appeared. The rationale of thymus therapy for myasthenia gravis is predicated on the high incidence of pathologic thymus glands reported to be associated with this condition.[2] There is as yet no certain evidence which will permit the establishment of a thymus-thyroid connection. Neither can the possibility of such a connection be wholly excluded. It is worthy of note in this connection that Rowntree,[3] using the same thymus extract preparation, has in over 100 cases in which various conditions were treated found no instance of hyperthyroidism following its use.

The simultaneous occurrence of hyperthyroidism and myasthenia gravis in the same patient seems to be relatively rare, although Buzzard [4] mentioned it as a common occurrence. Of 24 reported cases of hyperthyroidism in which palsy of the extraocular muscles occurred, only 7 [5] appear to be instances of a combination of myasthenia gravis

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1a. The patient was not seen after Dec. 1, 1938 until March 5, 1939, at which time she was sent to the Graduate Hospital. She was moribund. She had been ill for one week with a grippal infection. Huge doses of prostigmine and guanidine failed to prevent death, which occurred in a respirator within six hours of admission.

2. Thorner, M. W., and Yaskin, J. C.: The Treatment of Myasthenia Gravis, Am. J. M. Sc. **194**:411, 1937.

3. Rowntree, L. G.: Personal communication to the author, 1938.

4. Buzzard, F. E.: Myasthenia Gravis, in Allbutt, T. C., and Rolleston, H. D.: System of Medicine, London, Macmillan & Co., 1910, vol. 7, p. 51.

5. (*a*) Voss, G.: Zur Symptomatologie und Therapie der Basedowschen Krankheit, Deutsche med. Wchnschr. **29**:590, 1903. (*b*) Meyerstein, R.: Ueber das kombinierte Vorkommen von Myasthenie und Basedowsche Krankheit, Neurol. Centralbl. **23**:1089, 1904. (*c*) Rennie, G. E.: Exophthalmic Goiter Combined with Myasthenia Gravis, Rev. Neurol. & Psychiat. **6**:226, 1908; M. J. Australia **2**:416, 1919; (*d*) Myasthenia Gravis with Exophthalmic Goiter, Rev. Neurol. & Psychiat. **11**:475, 1913. (*e*) Vedsmand, H.: Pluriglandular Insufficiency, Ugesk. f. læger **85**:405, 1923. (*f*) Wolff, H. G.; Keutmann, H., and Cobb, S.: The

(Footnote continued on next page)

and exophthalmic goiter. In the remaining 17 cases, 2 of the patients showed signs of involvement of the central nervous system,[6] probably in the nature of amyotrophic lateral sclerosis; the other 15 cases[7] were largely instances of external ophthalmoplegia occurring during the course of thyrotoxicosis with exophthalmos. Presumably the majority of isolated palsies of the extraocular muscles occurring in association with exophthalmic goiter are due to the mechanical distortion of the structures of the orbit or to other causes unrelated to myasthenia gravis. The presence of palsy of the extraocular muscles is not in itself pathognomonic of myasthenia gravis. Neither can the presence of lymphorrhages in the muscles be considered conclusive evidence of the presence of myasthenia gravis, for, as Dudgeon and Urquhart[8] have shown, these lymphocytic collections are present in 8 of 9 cases of exophthalmic goiter. More recently it has been shown that lymphorrhages are present in other conditions, such as myositis. The occurrence, however, of palsy of the extraocular muscles even in exophthalmic goiter is far from common. Heuer[7a] stated that in a series of 300 cases of exophthalmic goiter in only 1 case (which he reports) was there evidence of such paralysis. Since palsy of the extraocular muscles is not common in hyperthyroidism, one may

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Electromyogram in Myasthenia Gravis, Brain **51**:508, 1928. (*g*) Cohen, S. J., and King, F. H.: Relation Between Myasthenia Gravis and Exophthalmic Goiter, Arch. Neurol. & Psychiat. **28**:1338 (Dec.) 1932.

6. Burger, W.: Ueber Thyrotoxilsose mit spinalen Symptomen, Deutsches Arch. f. klin. Med. **162**:355, 1928. Sterling, W.: Maladie de Basedow, myasthénie, et amyotrophie progressive, Rev. neurol. **1**:93 (Jan.) 1930.

7. (*a*) Heuer, G. J.: The Cerebral Nerve Disturbances in Exophthalmic Goiter, Am. J. M. Sc. **151**:339, 1916. (*b*) Bristowe, J. S.: Cases of Ophthalmoplegia Complicated with Various Other Infections of the Nervous System, Brain **8**:313, 1885. Féreol, M.: Report of a Case, Gaz. hebd. de méd. **26**:112, 1889. Finlayson, J.: On the Paralysis of the Third Nerve as a Complication of Grave's Disease, Brain **13**:383, 1890. Maude, A.: A Case of Ophthalmoplegia with Grave's Disease, ibid. **15**:121, 1892. Posey, W. C.: Palsy of the Extraocular Muscles in Exophthalmic Goitre, Am. J. M. Sc. **128**:66, 1904. Kappis, M.: Ueber Gehirnnervenlähmungen bei der Basedowscher Krankheit, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **22**:657, 1910. Bernhardt, M.: Basedowsche Krankheit und Augenmuskellähmung, Neurol. Centralbl. **30**:706, 1911. McKendree, C. A.: A Case of Myasthenia Gravis, J. A. M. A. **63**:1553 (Oct. 31) 1914. den Boer, M.: Goiter with Total Ophthalmoplegia, Nederl. tijdschr. v. geneesk. **1**:2284, 1920. Jackson, A. S., and Bates, A. D.: Myasthenia Gravis, J. A. M. A. **81**:114 (July 14) 1923. Jaensch, P. A.: Augenmuskellähmungen bei Basedowscher Krankheit, Deutsche med. Wchnschr. **50**:1249, 1924. Wedd, M. A., and Permar, H. H.: Ophthalmoplegia in Grave's Disease, Am. J. M. Sc. **175**:733, 1928. Garvey, J. L.: Ophthalmoplegia and Grave's Disease, Ann. Int. Med. **3**:917, 1930. Schönberg, H.: Grenzfall von Morbus Basedowii und Myasthenia gravis pseudoparalytica, Deutsche med. Wchnschr. **63**:738, 1937.

8. Dudgeon, L. S., and Urquhart, H. L.: Lymphorrhages in Exophthalmic Goiter, Brain **49**:182, 1926.

safely assume that the coexistence of myasthenia gravis and exophthalmic goiter is very rare, as the vast majority of patients with myasthenia gravis have such paralysis. As Naffziger [9] pointed out, the palsies of the extraocular muscles encountered with hyperthyroidism are chiefly associated with exophthalmos, which was never present in the case here presented.

In the case reported here it was evident that when the manifestations of hyperthyroidism were at their height the symptoms of myasthenia gravis were at a minimum, and as the thyrotoxicosis waned the myasthenia reappeared. In the case reported by Wolff, Keutmann and Cobb [5f] the myasthenia did not appear until after thyroidectomy, and then the patient's periods of the greatest strength coincided roughly with the periods in which the basal metabolic rate was highest. The patient in the case reported by Cohen and King [5g] showed evidence of exophthalmic goiter and received roentgen therapy over the thyroid gland. It was only after this irradiation and the consequent reduction in the basal metabolic rate that the symptoms of myasthenia appeared.

The fact that abnormalities of the thymus gland occur in 50 per cent of cases both of myasthenia gravis [10] and of exophthalmic goiter [11] has been used to link the two conditions. But whereas in exophthalmic goiter the abnormality consists of persistence or simple hyperplasia of the thymus gland, in myasthenia gravis thymic neoplasms of various types are usually found.

All these factors, the extreme rarity of cases in which the two diseases coexist, the fact that in these rare cases a "seesaw" type of balance seems to occur and the fact that the administration of a sufficient amount of potent thyroid extract to a myasthenic patient effected a reduction of myasthenic symptoms, appear to support a hypothesis that the two diseases are mutually antagonistic. The thymic abnormalities and the lymphorrhages which occur in both diseases are not sufficiently pathognomonic of either condition to be proof of any similarity in the two.

SUMMARY AND CONCLUSIONS

A case of myasthenia gravis is presented in which the appearance of hyperthyroid symptoms was attended by a lessening of the myasthenic symptoms. The administration of thyroid substance to a patient with

9. Naffziger, H. C.: Progressive Exophthalmos Associated with Disorders of the Thyroid Gland, Ann. Surg. **108**:529, 1938. Lymphorrhages in Ocular Muscles: "One of the patients suffered from myasthenia in addition to exophthalmic goiter."

10. Norris, E. H.: Thymoma from Unusual Case of Myasthenia Gravis, with Observations on General Pathology, Am. J. Cancer **30**:308, 1937.

11. Means, J. H.: The Thyroid and Its Diseases, Philadelphia, J. B. Lippincott Company, 1937, p. 289.

uncomplicated myasthenia gravis coincided with a period of remission of the myasthenic symptoms. In two cases previously reported by others [5f,g] there was some evidence of this same type of "seesaw" balance between myasthenia gravis and exophthalmic goiter. For these reasons it is suggested that the two diseases are mutually antagonistic. Lastly, it is felt that this relation is a matter of scientific, but not of immediate therapeutic, importance.

HEART FAILURE IN SUBACUTE BACTERIAL ENDOCARDITIS

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Heart failure is often regarded as one of the important negative features of subacute bacterial endocarditis. Attention has been repeatedly directed to the absence of myocardial insufficiency in the disease. In this respect subacute bacterial endocarditis has been contrasted with rheumatic carditis, in which heart failure may be prominent in the clinical picture and may exist in a chronic and advanced form. However, it is generally admitted that heart failure may make its appearance during the late stages of the disease. Toxemia, a prominent factor in subacute bacterial endocarditis, has commonly been considered causal.

A short outline of the literature concerning the role of heart failure in subacute bacterial endocarditis is given in this paper, and the opinions on the character and extent of the anatomic changes in the myocardium in this disease are discussed. Observations in 40 cases of subacute endocarditis are presented, with special attention to evidence of heart failure and anatomic changes in the heart. A short discussion of these findings concludes the study.

REVIEW OF LITERATURE

Horder [1] wrote that arrhythmia, symptoms of inadequate response to effort, signs of dilatation of the heart and the results of so-called decompensation not only may be conspicuous by their absence but are unusual. He also stated that there is some difference in the views of different observers as to the relative incidence of the classic signs and symptoms of heart failure toward the end of the course of the disease. He stressed that there is general agreement that for the major part of its course subacute bacterial endocarditis is largely destitute of cardiac features.

From the Departments of Internal Medicine and Pathology, the Michael Reese Hospital.

Presented at the eleventh annual meeting of the Central Society for Clinical Research, Chicago, Nov. 4, 1938.

1. Horder, T.: Discussion on the Clinical Significance and the Course of Subacute Bacterial Endocarditis, Brit. M. J. **2**:301, 1920.

Libman [2] stated that it is a remarkable fact that in many cases of the usual type there are no evidences of cardiac insufficiency until late in the course of the disease. In that less frequently encountered condition designated as the "bacteria-free stage" of subacute bacterial endocarditis, he noted [3] that myocardial insufficiency is a much more marked feature than it is in the active bacterial stage.

Thayer [4] expressed the opinion that the terminal features of infective endocarditis are generally those of grave septicemia. He observed striking myocardial insufficiency in only one fourth of 99 cases in which he followed the disease to a fatal termination.

Lewis [5] remarked that cardiac failure with congestion is rarely present in the early stages of this disease but is so frequent in the later stages as to be one of the chief causes of death.

A number of other clinical observers have expressed agreement with the foregoing opinions.[6]

Only a few investigators have made a study of the myocardial lesions associated with subacute bacterial endocarditis. The contributions of the following authors represent existing opinions:

Lewis [5] stated that there are no recognizable lesions in the heart muscle.

Libman [7] remarked that the essential lesion in the myocardium is an interstitial round cell infiltration, the so-called Bracht- Wächter bodies, that the lesions are not present in all cases and that they are not specific.

Starling [8] stated that the myocardium does not suffer severely, despite the frequent observation of scattered foci of myomalacia with cellular infiltrations.

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2. Libman, E.: The Clinical Features of Subacute Streptococcus (and Influenzal) Endocarditis in the Bacterial Stage, M. Clin. North America **2**:117, 1918.

3. Libman, E.: A Consideration of the Prognosis in Subacute Bacterial Endocarditis, Am. Heart J. **1**:25, 1925.

4. Thayer, W. S.: Observations on Rheumatic Pancarditis and Infective Endocarditis, Ann. Int. Med. **5**:247, 1931.

5. Lewis, T.: Diseases of the Heart, ed. 2, New York, The Macmillan Company, 1937.

6. (*a*) White, P. D.: Heart Disease, ed. 2, New York, The Macmillan Company, 1937. (*b*) Blumer, G.: Subacute Bacterial Endocarditis, Medicine **2**: 105, 1923. (*c*) Fishberg, A. M.: Heart Failure, Philadelphia, Lea & Febiger, 1937. (*d*) Laws, C. L., and Levine, S. A.: Clinical Notes on Rheumatic Heart Disease with Special Reference to the Cause of Death, Am. J. M. Sc. **186**:833, 1933. (*e*) Cotton, T. F.: Subacute Infective Endocarditis, Brit. M. J. **2**:851, 1920.

7. Libman, E.: Characterization of the Various Forms of Endocarditis, J. A. M. A. **80**:813 (March 24) 1923.

8. Starling, H. J.: Endocarditis Lenta, Quart. J. Med. **16**:263, 1922.

Without reference to the type and character of the anatomic change, Longcope [9] mentioned that some form of lesion may be observed in one-half the cases in which autopsy is performed.

Blumer [6b] stated that chronic interstitial myocarditis was noted in 8 of 150 hearts, acute myocarditis in 2, small abscesses in 3 and focal necrosis and infarcts each in 2.

The contributions of Clawson,[10] which appeared a decade ago, are noteworthy in emphasizing the extensive inflammatory change occurring in the heart muscle in subacute bacterial endocarditis. Clawson stated that myocarditis is more frequent in subacute bacterial endocarditis than in acute and recurrent rheumatic endocarditis and that the greater frequency of abscesses in subacute bacterial endocarditis than in other forms of endocarditis is accounted for by the lodging in the myocardium of infected emboli from the valves.

One of us (Saphir [11]) described fairly widespread inflammatory and degenerative changes consisting chiefly of focal necrosis, minute infarcts, Aschoff bodies and perivascular fibrosis. The most frequent and characteristic lesions were minute infarcts.

In summary, the following two points are brought out: 1. Heart failure frequently accompanies subacute bacterial endocarditis but is present during only a small fraction, usually the terminal part, of its course. The emphasis is clearly on the lack of any appreciable part played by it in the general course of the disease. 2. In descriptions of the character and extent of the myocardial lesions in this disease one notes a great diversity of opinion. In fact, observations indicate a gamut of changes ranging from none at all to changes of considerable severity and magnitude, the general opinion being that the structural alterations are without much significance.

It seems a remarkable fact, too, that the literature discloses few studies of the extracardiac lesions which would denote the existence of previous heart failure of some intensity and chronicity. We refer to the presence of chronic passive hyperemia of the lungs, liver and other viscera. Such evidence, when of sufficient grade, connotes heart failure and affords information highly pertinent to the question. Blumer found such evidence and reported chronic passive hyperemia of the lungs in 30 cases and of the liver in 53.

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9. Longcope, W. T.: The Differentiation of Acute Rheumatic Fever from Bacterial Endocarditis, M. Clin. North America **16**:1029, 1933.

10. Clawson, B. J.: Myocarditis, Am. Heart J. **4**:1, 1928.

11. Saphir, O.: Myocardial Lesions in Subacute Bacterial Endocarditis, Am. J. Path. **11**:143, 1935.

MATERIAL AND METHODS

Ten of the 40 patients with subacute bacterial endocarditis came under our clinical observation. The clinical data on 30 cases were furnished solely by the hospital records. It becomes a matter of great importance to find in these records clearcut descriptions of the objective findings indicating beyond question the presence of heart failure. Since the expression heart failure is used to designate clinical states varying between those showing only signs of exhaustion of the cardiac reserve and those exhibiting advanced congestive failure, it was thought advisable to consider only cases in which objective signs were present as those of heart failure. Edema of the dependent parts, fluid in the serous sacs, rales over the bases of the lungs and hepatic enlargement were relied on as signs necessary for the diagnosis of heart failure. It is, of course, difficult to affix a definite time to the advent of heart failure in a patient by studying the record alone. To admit less error and to conform to the scope of this paper, we made the diagnosis only when the objective symptoms were of a magnitude indicating beyond doubt the presence of the condition. The possibility of edema of renal origin has been excluded as carefully as possible.

It becomes necessary to define the disease process itself. What is subacute bacterial endocarditis? We are aware of the fact that anatomically subacute bacterial endocarditis may be difficult to differentiate from acute bacterial endocarditis. From our experience, based on combined clinical and anatomic observations, we have set forth certain diagnostic criteria, the presence of a majority of which is taken to favor the diagnosis of subacute bacterial endocarditis. These criteria are as follows: (1) large vegetations; (2) evidence of old valvular lesions (rheumatic, nonspecific, syphilitic or congenital malformations); (3) involvement of the adjacent mural, auricular and ventricular endocardium and the chordae tendineae; (4) minute ulcerations of the cusps or leaflets of the valve, and (5) the presence of cocci in chains in sections of the vegetations.

An autopsy was performed in every instance, and special attention was given to the valvular changes in the heart and to the gross and histologic appearance of the myocardium, lungs, liver, spleen and kidneys. Blocks were taken from these organs, fixed in solution of formaldehyde and embedded in paraffin. Most commonly the hematoxylin-eosin stain was used, though special stains were employed when necessary. A more detailed histologic study of the myocardium of some of these hearts has been reported previously.[11]

The principal organs examined for chronic passive hyperemia were the lungs, liver, spleen and kidneys. The degree of chronic passive hyperemia in these organs was judged arbitrarily, the changes being classified as 1 plus, 2 plus, etc. In the lungs, for instance, the amount of connective tissue proliferation, the relative number of heart failure cells and the presence of red blood cells determined the stage of chronic passive hyperemia. In the liver the extent of dilatation of the sinusoids, the accompanying changes in the liver cells and the amount of connective tissue in the periportal spaces were used in the determination of the degree of chronic passive hyperemia. It should be stressed in this connection that whenever there was the slightest doubt as to the classification of the degree of passive hyperemia of the various organs, the condition was placed in the lower of the two categories in question.

RESULTS

Eighteen, or 45 per cent, of our 40 patients showed frank clinical signs of heart failure, such as distention of the veins of the neck, edema

of the dependent parts, enlargement of the liver, fluid in the serous sacs and rales at the bases of the lungs. In all of these 18 patients autopsy revealed chronic passive hyperemia of the viscera, and most of them had appreciable collections of fluid in the serous sacs. Heart failure of an advanced grade was exhibited clinically by 11 of these 18 patients. In the other 22 patients there were no clinical signs of myocardial insufficiency. In 12 of the 22 patients autopsy showed a grade of chronic passive hyperemia of the lungs, liver and other viscera hardly less than that seen in the former group of 18 patients. A few of the aforementioned 12 patients had accumulations of fluid in the serous sacs that escaped clinical recognition. This is taken as evidence that heart failure of some grade must have been present for some time before death. For the groups studied clinically and that studied pathologically the frequency of heart failure was 75 per cent. The remaining 9 patients had no chronic passive hyperemia and no clinical evidence of heart failure.

Eight patients seen for the first time were observed to have heart failure at the time of their admission to the hospital; in 10 the development of heart failure was noted during the course of the disease. In all instances in which heart failure was observed it was continuous and progressive and extended from two weeks to two months. Five of the 8 patients admitted to the hospital with heart failure died approximately one week after admission; the remaining 3 had heart failure for a period roughly between one and two and one-half months. The average duration of the disease in 18 patients with heart failure was eight months; in the remaining patients it was approximately five months. The clinical course of 6 of the 10 patients in whom no chronic passive hyperemia of the organs was present was abruptly terminated by embolic accidents.

All the hearts with gross lesions typical of subacute bacterial endocarditis invariably showed large vegetations and evidence of older endocardial lesions. Also, the mural endocardium was always involved. Except in 2 hearts, the underlying lesions of the endocardium were those of either true rheumatic endocarditis or of endocarditis the cause of which could not be determined but which resembled morphologically the rheumatic type. In 1 of the 2 exceptions the heart was the seat of a congenital anomaly (patency of the intraventricular septum, and foramen primum). Most of the vegetations were seen in the vicinity of the defects. In the second instance there was syphilitic aortitis with involvement of the aortic valve.

Generally the myocardium grossly was light grayish brown, and often yellow dots and streaks were seen, suggesting fatty degeneration of the myocardium. In some instances on section the myocardium seemed bulging. Its normal architecture was obscured. Grayish dots and streaks were especially clear in the wall of the left ventricle.

Most of the gross evidence of chronic passive hyperemia at autopsy was in the liver and the lungs. The passive hyperemia in the spleen and in the kidneys was sometimes obscured by acute hyperplasia of the spleen and acute nephritis, respectively. The degree of chronic passive hyperemia in the various organs is given in table 1.

Histologic examination of the myocardium revealed significant changes. In 14 instances abscesses were seen in the myocardium; most commonly that of the left ventricle was involved, and occasionally the intraventricular septum close to the endocardium of the left ventricle. Often areas of necrosis were seen, with only a few polymorphonuclear leukocytes. These foci of necrosis were interpreted as early abscesses. Occasionally polymorphonuclear leukocytes were seen in the interstitial

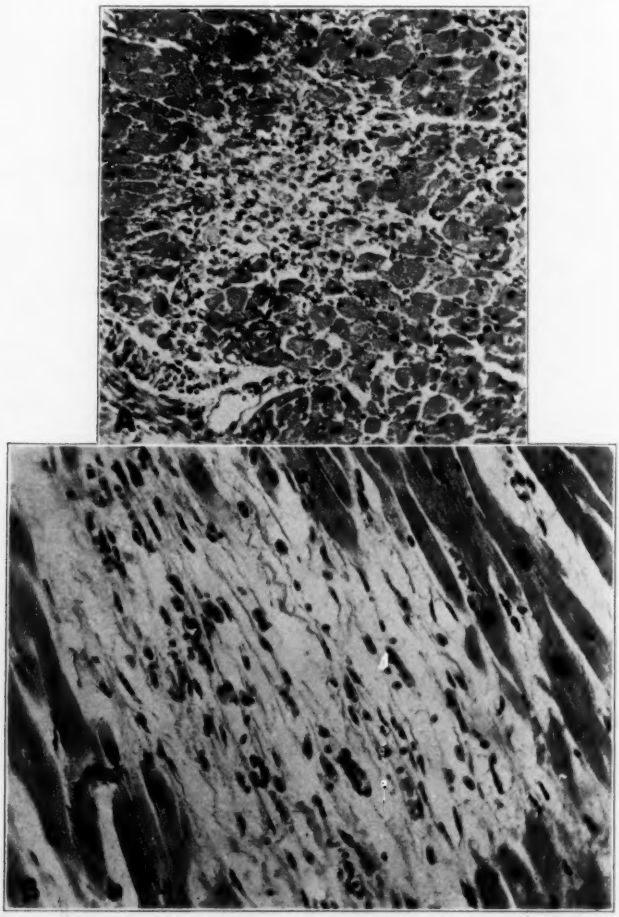
TABLE 1.—*Degree of Chronic Passive Hyperemia*

Case No.	Lungs	Liver	Spleen	Kidneys	Case No.	Lungs	Liver	Spleen	Kidneys
1	+	+	—	—	21	++	++	—	—
2	++	++	++	+	22	++++	+++	++	+
3	++	++	+	+	23	—	—	—	—
4	++	++	++	+	24	+++	++	++	—
5	++++	++++	++++	+++	25	+	+	—	—
6	+++	+++	+++	++	26	—	+	+	—
7	—	—	—	—	27	++	+	+	—
8	+++	++++	+++	++	28	+	++	+	—
9	—	+	+	—	29	—	+	+	—
10	—	—	—	—	30	++	++	+	—
11	+++	++	+	—	31	++++	++++	+++	+
12	++	++++	+++	++	32	+++	++	+++	—
13	+++	+++	+++	+	33	+++	+++	++	+
14	++	++	+	—	34	—	—	—	—
15	++	++	++	—	35	—	—	—	—
16	++	+++	++	+	36	++	+++	+++	+
17	++	++	++	+	37	++	++	++	—
18	+++	++++	++++	++	38	+++	+++	+++	+
19	++++	++++	+++	—	39	++++	++++	++++	++
20	++++	++++	+++	+	40	+++	++	++	+

tissue, close to the blood vessels, but areas of necrosis were negligible in these regions. Perivascular areas of subacute and chronic inflammation were also encountered. Often the inflammatory cells were mainly lymphocytes, and occasionally a few polymorphonuclear leukocytes were intermingled with the lymphocytes. Perivascular fibrosis was rather common. It was observed in those hearts which showed Aschoff bodies but also was occasionally present in the absence of Aschoff bodies. In 15 instances Aschoff bodies were observed in the myocardium. Only cellular accumulations which unquestionably were typical Aschoff bodies, as described in a previous study,[12] were so designated. They were typically located in a perivascular situation and were observed to be independent of other changes in the same heart. The most consistent changes in the myocardium were the replacement of heart muscle fibers

12. Saphir, O., and Wile, S. A.: Rheumatic Manifestations of Subacute Bacterial Endocarditis in Children, Am. Heart J. **9**:29, 1933.

by many spindle-shaped cells with a few lymphocytes and a number of phagocytic cells, the cytoplasm containing granules of brown pigment. Often a scant new formation of connective tissue fibers and small



A (× 150), minute infarct in the myocardium; *B* (× 250), organizing infarct in the myocardium. Hematoxylin-eosin preparation.

Lesions like these are most frequently encountered in the myocardium of patients with subacute bacterial endocarditis.

blood vessels was also present in these regions. These areas could easily be interpreted as organizing infarcts. A diligent search sometimes revealed emboli in the smaller branches of the coronary arteries in

the vicinity of these regions. The emboli consisted most commonly of amorphous débris which morphologically resembled the superficial portions of vegetations. These infarcts were present in 27 instances. Table 2 shows the incidence of abscesses, Aschoff bodies, minute infarcts, emboli, perivascular fibrosis and inflammatory changes in the myocardium. It also gives the degree of chronic passive hyperemia

TABLE 2.—*Myocardial Changes in Subacute Bacterial Endocarditis*

Case No.	Age, Yr.	Clinical Evidence of Heart Failure	Foci of Necrosis and Abscesses	Minute Infarcts	Emboli	Aschoff Bodies	Perivascular Fibrosis	Acute and Chronic Inflammation	Chronic Passive Hyperemia in Various Organs*
1	5	..	+	..	..	+	..	Acute	0
2	19	..	..	+	..	+	+	.....	+
3	50	..	+	+	+	..	..	.....	+
4	29	+	+	..	..	..	..	.....	+
5	33	+	..	+	..	+	+	.....	++++
6	19	+	+	+	+	..	..	Chronic	+++
7	19	..	+	+	+	+	..	.....	0
8	41	+	..	..	+	+	+	.....	+++
9	10	..	..	+	..	+	+	Chronic	0
10	13	..	+	+	+	+	+	.....	0
11	11	..	..	+	..	+	+	Chronic	++
12	29	+	..	+	..	..	+	.....	++
13	29	+	..	+	..	..	+	Chronic	+++
14	35	+	+	..	+	..	..	.....	+
15	32	+	+	+	+	..	+	.....	++
16	43	+	..	+	+	..	+	Chronic	++
17	46	..	..	..	..	..	+	Chronic	++
18	42	+	..	+	+	..	+	.....	++++
19	21	..	+	..	..	..	..	Acute	+++
20	62	+	..	+	..	..	..	.....	+++
21	13	..	..	..	..	+	+	.....	+
22	6	..	+	+	+	+	+	.....	++
23	23	..	..	+	+	..	..	Chronic	0
24	73	+	..	..	+	+	+	Chronic	++
25	48	..	..	+	..	..	..	.....	0
26	41	..	..	+	+	..	+	.....	0
27	25	+	+	..	+	+	+	Acute	+
28	47	..	+	..	..	..	+	.....	+
29	42	..	+	+	..	..	+	.....	0
30	51	..	+	..	..	..	+	Chronic	+
31	29	..	..	+	+	+	..	.....	+++
32	30	..	..	+	..	..	+	Acute	++
33	32	+	..	+	..	..	..	Acute	++
34	38	..	..	+	+	..	..	Acute	0
35	38	..	..	+	+	+	+	.....	0
36	15	..	..	+	+	+	..	Acute	++
37	50	+	..	..	..	..	+	Acute	++
38	19	+	..	+	+	..	..	Acute	+++
39	29	+	..	+	+	..	..	.....	++++
40	42	+	..	..	..	..	..	Chronic	++

* In determining the degree of chronic passive hyperemia the amount of free fluids in the various cavities was also taken into consideration.

which was observed in the various organs and states whether or not there was clinical evidence of heart failure.

An analysis of this table indicates that there is no relation between the presence of Aschoff bodies, abscesses or infarcts and chronic passive hyperemia as demonstrated at autopsy. In some instances in which Aschoff bodies were observed in the myocardium there was only slight chronic passive hyperemia in the various organs, while in other instances in which the myocardium showed a variety of anatomic lesions exclusive

of Aschoff bodies chronic passive hyperemia was severe. Extensive infarction of the heart following coronary embolism occurred in 1 case. The patient exhibited advanced congestive heart failure of two months' duration.

It may be of interest to emphasize that Aschoff bodies were observed in 15 hearts, an incidence of 37 per cent; 9 of the patients were under 20 and 6 were over 25 years of age. In only 3 these 15 patients was heart failure observed clinically. At autopsy chronic passive hyperemia was observed in 10 of the 15 cases, an incidence practically the same as that for the entire series of 40 cases.

COMMENT

From an examination of our data two pertinent facts are brought out: first, that heart failure occurs more frequently in subacute bacterial endocarditis than is commonly believed, and, second, that the heart muscle is the seat of widespread anatomic change.

It will be readily appreciated that because of lack of unanimity of opinion concerning the anatomic relation, confusion must exist in the explanations of the cause of heart failure, which we have noted to occur so frequently in this disease. Those who maintain that the heart shows no or minimal change must necessarily advance some explanation for the failure on the basis of function, and these explanations have not been wanting. Frequently one encounters statements to the effect that "poisoning," "exhaustion," "strain" or a combination of these is causal. On the other hand, those who realize, as we do, that there are ample structural alterations to explain the occurrence of heart failure may readily place it on an anatomic basis.

While it is true that arterial embolism, sepsis, toxemia and cachexia are the cardinal symptoms of the disease, heart failure of some grade and chronicity has to be reckoned with as a feature of the disease. Our material is too meager to controvert the rather common opinion that it is a terminal event. The average duration of the disease in our series was only a little over six months. In point of absolute duration, the heart failure occurring in subacute bacterial endocarditis must necessarily be relatively short, although our data indicate chronicity of some degree. This ratio may compare favorably with that for other inflammatory and degenerative diseases of the heart requiring a decade or two for their resolution. It would be intriguing, if it were possible, to discern major differences in the clinical pattern in the different forms of heart disease. There has been so much emphasis on the absence of heart failure in subacute bacterial endocarditis until the very late stages that a "pattern" here appears well defined. After critical examination of what has been said on this matter and analysis of our own data it is difficult to discern real differences between the disease under discussion

and other forms of heart disease. In the presentation of a series of cases so limited as this the question arises as to whether they are "representative," for the disease is one of great variability and is often shortened by embolic accidents. On this point it may be said that many reports dealing with the subject are based on series no larger than ours.

The lack of significant alterations in the electrocardiograms of patients with subacute bacterial endocarditis has further supported the popular contention that the heart muscle escapes any significant structural change in this disease. In the electrocardiographic studies of Rothschild, Sacks and Libman [13] and also in those of Levy and Turner,[14] this feature has been contrasted with the observations in cases of rheumatic infection, in which abnormalities in the ST segment and other electrocardiographic changes are frequently noted in serial curves. In commenting on this point, Swift [15] accepted this as evidence of the "lack of parenchymatous irritation" in the heart in subacute bacterial endocarditis. From the conclusions reached by Rothschild, Sacks and Libman [13] one can only infer that serial curves were obtained on patients with subacute bacterial endocarditis, though the authors have clearly indicated that they were obtained on patients in the rheumatic group. Levy and Turner [14] were careful to state that graphic records for the nonrheumatic group were secured at less frequent intervals. They studied the records of only 23 patients with subacute bacterial endocarditis and compared them with those of 403 patients comprising the rheumatic group. With the disproportionately large number of patients in the latter who were followed more systematically, it is obvious that no conclusions as to the comparative frequency of electrocardiographic alterations in the two groups may be justly drawn. With lesions so widespread as we found them in the myocardium a high incidence of electrocardiographic alterations might be expected to be found in serial curves. Unfortunately, our material is too fragmentary to make possible any comment except that significant changes in the ST segment and the T wave were observed in the few cases so studied. If the Aschoff bodies are responsible for the fleeting changes seen in the electrocardiogram in acute rheumatic infection (Cohn and Swift [16] admitted this possibility), it may be pertinent to ask why Aschoff bodies in the myocardium in cases of subacute bacterial endocarditis should not cause

13. Rothschild, M. A.; Sacks, B., and Libman, E.: The Disturbances of the Cardiac Mechanism in Subacute Bacterial Endocarditis and Rheumatic Fever, Am. Heart J. **2**:356, 1926.

14. Levy, R. L., and Turner, K. B.: Impaired Auriculoventricular Conduction in Rheumatic Fever: A Comparative Study with Diagnostic Applications, Arch. Int. Med. **43**:267 (Feb.) 1929.

15. Swift, H. F.: The Heart in Infection, Am. Heart J. **3**:629, 1928.

16. Cohn, A. E., and Swift, H. F.: Electrocardiographic Evidence of Myocardial Involvement in Rheumatic Fever, J. Exper. Med. **39**:1, 1924.

similar electrocardiographic changes. This question is raised merely for argument, for apart from the presence of Aschoff bodies, which are frequently seen in association with subacute bacterial endocarditis (they were present in 37.5 per cent of our cases), there are other lesions which might readily produce all the fleeting electrocardiographic changes seen in cases of rheumatic disease. It also may be worth while to comment that when this study was first undertaken it was thought that the coexistence of specific rheumatic infection and subacute bacterial endocarditis would serve as a clue to the development of heart failure in the latter disease, a presumption which was not borne out.

The study of the myocardium clearly indicates why heart failure was present in some instances. As a matter of fact, in the light of these investigations it seems remarkable that chronic passive hyperemia was not more pronounced than it was, because of the severe changes in the myocardium in almost every instance. It is remarkable that the myocardium may be as severely damaged as in some of our cases and chronic passive hyperemia be relatively slight. From this study it also seems clear that there is no distinct relation between anatomic myocardial changes and clinical evidence of heart failure. From the anatomic point of view, moreover, it is difficult to believe that a patient whose myocardium is so severely damaged does not show more clinical evidence of myocardial failure. On the other hand, when heart failure was present in these cases of subacute bacterial endocarditis, anatomic changes in the myocardium were invariably observed. It seems evident that in some patients with severe myocardial changes the reserve power of the undamaged myocardial fibers is so great that there is little evidence of heart failure and, vice versa, that in other patients with fewer anatomically demonstrable myocardial changes the reserve power of the apparently unharmed muscle is so limited that heart failure ensues. Of course, the presence of toxemia with dilatation of the capillary bed should also be considered in explanation of the heart failure; but it seems probable that such hypothetic paralysis of the vascular bed is present in all cases of subacute bacterial endocarditis, with severe or with less severe myocardial lesions. Yet some of the patients die with no or with slight clinical evidence of heart failure, while others exhibit evidence of severe heart failure. It seems, therefore, that there is no relation between heart failure and demonstrable damage of the myocardium. It appears, rather, that the state of the apparently undamaged muscle determines whether the myocardium in these instances becomes insufficient or whether it is able to maintain its function. To this intangible and varying reserve power of the uninvolved muscle fibers, which also governs the fate of the infarcted arteriosclerotic heart, must be ascribed the apparent discrepancy between clinically observed heart failure in one patient and its absence in another.

SUMMARY AND CONCLUSIONS

Heart failure of a fairly advanced grade was seen in 18 of 40 patients with subacute bacterial endocarditis, a clinical frequency of 45 per cent. At necropsy the various organs showed a marked degree of chronic passive hyperemia in every instance, and there were frequently accumulations of fluid in the serous sacs.

The presence of marked chronic passive hyperemia of the lungs, liver and other viscera in 12 additional patients in whom the heart failure was not recognized clinically indicates that here, too, it must have been present for some time. The combined frequency of heart failure for the groups studied pathologically and that studied clinically was 75 per cent.

Ten patients had no chronic passive hyperemia. The clinical course of 6 of these was terminated by the rupture of mycotic aneurysms.

Extensive myocardial lesions are observed uniformly in patients who die of subacute bacterial endocarditis. They consist of minute emboli, infarcts and abscesses, diffuse inflammation, Aschoff bodies and perivascular fibrosis.

These structural alterations are adequate to explain the advent of heart failure in this disease. They are of such magnitude and intensity as to make it remarkable that heart failure is not even more marked than we found it to be.

It is not necessary to invoke such general causes as toxemia or exhaustion to explain the advent of heart failure in subacute bacterial endocarditis.

The coexistence of rheumatic myocarditis and subacute bacterial endocarditis cannot be considered causal in the development of heart failure.

CLINICAL SIGNIFICANCE OF VARIATIONS IN SERUM PHOSPHATASE IN HEPATIC AND BILIARY DISORDERS

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During the eight years that followed Roberts'[1] observation of an increase in serum phosphatase in the presence of jaundice, numerous statistical studies and many experiments have been carried on to evaluate it as an aid in differential diagnosis. The mechanism accounting for the rise in serum phosphatase has not been satisfactorily described. Roberts stated that there is a pronounced increase in phosphatase in obstructive and in catarrhal jaundice. He suggested that this denotes nothing more than an expression of the presence of bile constituents in the blood, since bile itself has a high phosphatase content. In 1933 he[2] stated that this premise does not explain all the facts. He reached the conclusion, based on a study of 52 cases, that toxic, infective and catarrhal jaundice may be readily distinguished from jaundice of the obstructive type by characteristic values of phosphatase.

Subsequent investigators have not found this to be the case in the two types of jaundice. A review of the literature can be found in the articles by Greene, Shattuck and Kaplowitz,[3] Rothman, Meranze and Meranze,[4] Cantarow and Nelson[5] and Flood, Gutman and Gutman.[6] Some of the

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1. Roberts, W. M.: Variations in the Phosphatase Activity of the Blood in Disease, Brit. J. Exper. Path. **11**:90, 1930.

2. Roberts, W. M.: Blood Phosphatase and the van den Bergh Reaction in the Differentiation of the Several Types of Jaundice, Brit. M. J. **1**:734, 1933.

3. Greene, C. H.; Shattuck, H. F., and Kaplowitz, L.: Phosphatase Content of Blood Serum in Jaundice, J. Clin. Investigation **13**:1079, 1934.

4. Rothman, M. M.; Meranze, D. R., and Meranze, T.: Blood Phosphatase as an Aid in the Differential Diagnosis of Jaundice, Am. J. M. Sc. **192**:526, 1936.

5. Cantarow, A., and Nelson, J.: Serum Phosphatase in Jaundice, Arch. Int. Med. **59**:1045 (June) 1937.

6. Flood, C. A.; Gutman, E. B., and Gutman, A. B.: Phosphatase Activity, Inorganic Phosphorus and Calcium of Serum in Disease of the Liver and Biliary Tract: Study of One Hundred and Twenty-Three Cases, Arch. Int. Med. **59**:981 (June) 1937.

investigators have substantiated the findings of Roberts, namely, that the serum phosphatase value is greater than 10 units in cases of obstructive jaundice while in the hepatocellular form of jaundice, which includes the toxic and the infective type, the value is 10 units or less. Rothman and his co-workers found this test to be of greater clinical value than any other available test in differentiating between obstructive and non-obstructive jaundice. Other investigators, however, found such variable results in cases of hepatocellular jaundice that they concluded the test to be unreliable. For example, Cantarow and Nelson found that the serum phosphatase was below 10 units in 24 per cent of 50 cases of obstructive jaundice and in 36.6 per cent of 41 cases of hepatocellular jaundice, an observation which limits the practical significance of serum phosphatase from the standpoint of differential diagnosis.

The results of experimental procedures also have not been constant. By ligating the common bile duct in dogs, Bodansky and Jaffe,[7] Armstrong, King and Harris[8] and Thannhauser and his co-workers[9] produced a marked and progressive rise in serum phosphatase. A similar procedure in cats did not cause a rise. Hartman and Schelling,[10] Armstrong and King[11] and Freeman, Chen and Ivy[12] produced hepatic damage by different methods and noticed an increase in the serum phosphatase.

Flood and his colleagues[6] suggested that some of these inconsistencies may be due to the method used in estimating phosphatase activity. They pointed out that there are important differences in the classifications of jaundice employed by various investigators, as well as in the criteria considered necessary for definitely establishing the cause and type of jaundice. They finally pointed out the difficulty of drawing a sharp distinction between obstructive and hepatocellular jaundice for diagnostic purposes; it is probable that in the latter disorder also obstruction plays some role.

7. Bodansky, A., and Jaffe, H. L.: Phosphatase Studies: Increase of Serum Phosphatase After Bile Duct Ligation in the Dog, Proc. Soc. Exper. Biol. & Med. **31**:1179, 1934.

8. Armstrong, A. R.; King, E. J., and Harris, R. I.: Phosphatase in Obstructive Jaundice, Canad. M. A. J. **31**:14, 1934.

9. Thannhauser, S. J.; Reichel, M.; Grattan, F. J., and Maddock, S. J.: The Effect of Experimental Total Biliary Obstruction on the Serum Phosphatase Activation in Dogs and Cats, J. Biol. Chem. **121**:697, 1937.

10. Hartman, F. W., and Schelling, V.: Serum Phosphatase in Experimental Insufficiency of the Liver, Arch. Path. **18**:594 (Oct.) 1934.

11. Armstrong, A. R., and King, E. J.: Serum Phosphatase in Toxic and Hæmolytic Jaundice, Canad. M. A. J. **32**:379, 1935.

12. Freeman, S.; Chen, Y. P., and Ivy, A. C.: On the Cause of the Elevation of Serum Phosphatase in Jaundice, J. Biol. Chem. **124**:79, 1938.

Cantarow and Nelson [5] stated the belief that it is useless in the present state of knowledge to speculate about the possible mechanism which produces an increase of serum phosphatase in obstructive and hepatocellular jaundice. They pointed out that an increase cannot be explained, as implied by Herbert,[13] on the basis of obstruction to the flow of bile, either extrahepatic or intrahepatic. Cases in which the icterus index is high in the presence of a normal value for serum phosphatase and in which serum phosphatase values are increased in the presence of a normal icterus index were reported by Greene and his colleagues [3] and others. Rothman and his co-workers [4] pointed out the importance of the relation of serum phosphatase to the icterus index as an aid in differential diagnosis. A value of about 10 units for serum phosphatase in the presence of an increasing icterus index points toward a hepatocellular disorder.

Thannhauser and his co-workers [14] threw much light on this subject by a series of experiments on dogs and cats and experiments in vitro. They interpreted the rise in serum phosphatase after biliary obstruction as due to increased activation of the enzyme and not to actual increase in the amount of circulating phosphatase as previously supposed. The bile of dogs contains from 25 to 55 units of phosphatase per hundred cubic centimeters, an indication of almost complete activation of the phosphatase in gallbladder bile. After producing a complete biliary fistula, the authors found a paradoxic increase in serum phosphatase. Further experiments demonstrated the ability of bile salts to decrease the activation of serum phosphatase. They concluded that what has always been regarded as an increase in the serum phosphatase in the presence of disease is not an actual increase in enzyme but merely an activation of phosphatase normally present. The mechanism of activation in jaundice is dependent on an activating substance (a cofactor, or coenzyme, which has not yet been isolated or identified) and a depressing substance (like bile salts). Therefore, when there is an obstruction damming up both, since the cofactor is more powerful as an activating agent than the bile acids as depressors, the net result is an increase in the activity of serum phosphatase. The authors stated that the resultant activation of phosphatase must represent the outcome of reactions in a complex system consisting of enzyme, oxidation-reduction potential and substrate. Human disease may therefore originate from an excess of any of the factors in the system. However, the experimental basis of these conclusions has recently been questioned; therefore, they must

13. Herbert, F. K.: Plasma Phosphatase in the Various Types of Jaundice, Brit. J. Exper. Path. **16**:365, 1935.

14. Thannhauser, S. J.; Reichel, M., and Grattan, J. F.: Studies in Serum Phosphatase Activity, J. Biol. Chem. **121**:697, 1937.

be held in abeyance for the present (King and Delory [15] and Thannhauser, Reichel and Grattan [16]).

All investigators agree that serum phosphatase does not rise in cases of jaundice of purely hemolytic origin. It is on the application of this test as a means of differential diagnosis between hepatocellular and obstructive jaundice that the investigators disagree. In cases of obstructive jaundice the rise in serum phosphatase is fairly constant, and this fact has formed the basis of a valuable diagnostic test. This has been proved experimentally by ligating the common bile duct and noting the rise in serum phosphatase. In cases of hepatocellular jaundice, the results have been too variable to serve as a diagnostic aid, ranging from normal to increases of 50 units. The experimental procedures noted, produced to cause hepatic damage, have brought varying results, including marked increases. Thannhauser and Freeman, Chen and Ivy [12] even in the presence of a complete biliary fistula, noticed an increase in serum phosphatase. With the clinical observations and experimental results described, it has been a difficult and discouraging problem to account for the rise in serum phosphatase in order to use it as a clinical aid. The general confusion concerning this problem has been further increased by three types of clinical cases:

1. In some cases of cholecystitis, as reported by Cantarow and Nelson,[5] Greene and his co-workers [3] and confirmed in our studies, the icterus index is within normal limits or slightly elevated, but the value of serum phosphatase is increased even to 34 units. The cause for this increase has not been definitely explained hitherto.

2. In cases of congenital anomalies of the extrahepatic bile ducts in the newborn reported by Cantarow and Nelson [5] and Thannhauser,[17] in which the icterus index was markedly increased, the serum phosphatase values were, surprisingly, normal. This paradox, that obstruction exists and the serum phosphatase value is normal, has been difficult to explain.

It is interesting to note that here are two types of case in which the icterus index and serum phosphatase values do not show the usual relation. This has been noted before.

3. A third type of case exists, in which the biliary system is obstructed with resultant jaundice and the serum phosphatase value is normal or only slightly increased.

Correlation of the facts revealed by statistical data and experimental work has led to conclusions which have not always been consistent. For

15. King, E. J., and Delory, G. E.: Ascorbic Acid and Phosphatase Activity, Biochem. J. **32**:1157, 1938.

16. Thannhauser, S. J.; Reichel, M., and Grattan, J. F.: The Effect of Ascorbic Acid on Beta-Glycerophosphate, Biochem. J. **32**:1163, 1938.

17. Thannhauser, S. J.: Personal communication to the authors.

instance, it is known that the mucosa of the small intestine is relatively rich in phosphatase (Cantarow [18]). On the assumption that the enzyme passes into the portal stream through the same circuit as the bile pigments, even an hepatocellular obstruction should cause a constantly high serum phosphatase value if obstruction is the only factor involved. That this is not the case has already been shown. If all the phosphatase originates in the osseous system it is again difficult to explain its failure to rise in some cases of acute hepatitis when an obstruction is present as indicated by the accumulation of bile pigments in the blood stream. One might assume that the permeability of the cells of the liver through which the enzyme must pass is altered by certain constituents. The change in permeability may affect the enzyme or its activating substance in different ways, and this may account for the variable values in serum phosphatase.

The physiologic basis for the origin of this enzyme, its circulation and the influence of various substances on it, has been postulated by previous investigators. In addition to the physiologic factors, we [19] investigated the underlying pathologic changes which cause increased phosphatase values in the serum. This was done by experimental work on dogs. In this publication the result of an attempt at clinical correlation between the disorders of the liver and the biliary system and the variable serum phosphatase values is described. Clinical and experimental evidence indicate that the liver cells play no part in the formation of bile pigment but merely secrete it into the bile ducts. In the case of phosphatase metabolism, however, the liver plays more than a passive role, and this probably explains the different values in the hepatocellular type of jaundice.

On the basis of our experiments we concluded that the most likely explanation is the production of phosphatase or an activating substance by the liver; when the liver cell is damaged the production of the activating principle or actual enzyme is diminished. Accordingly, the rise in serum phosphatase in cases of hepatic and biliary disorders probably is dependent on two factors: (1) the state of the liver cells and (2) the degree of biliary obstruction. We attempted to apply these conclusions to cases of hepatic and biliary disease, in all of which the underlying pathologic conditions of the hepatic parenchyma were borne in mind.

In cases of extrahepatic obstruction, the hepatic parenchyma differs microscopically from that in cases of hepatocellular jaundice in which it is damaged to varying degrees. The presence of some obstruction to

18. Cantarow, A.: Review of Phosphatase Activity and Calcium and Electrolyte Metabolism, Internat. Clin. **1**:230, 1936.

19. Schiffmann, A., and Winkelman, L.: Influence of the Liver on Serum Phosphatase, Arch. Int. Med. **63**:919 (May) 1939.

the biliary system also in the latter condition has already been suggested by Flood and his colleagues.[6]

A table of illustrative cases of various hepatic manifestations, in the majority of which some degree of hepatocellular jaundice occurred is presented. All the laboratory tests are listed in order to provide a basis for comparison and to indicate that their adequacy is limited unless the underlying pathologic state of the liver also is taken into account.

Certain cases in which diagnostic difficulties were encountered are reported briefly.

CASE 6.—J. A., a 24 year old white man, was admitted to the hospital complaining of an insidious onset of jaundice for the past year and enlargement of the abdomen. On admission his temperature, pulse, respiration and blood pressure were normal. The liver and spleen were enlarged. The impression was that the patient had hypertrophic biliary cirrhosis (Hanot's type).

CASE 7.—L. A., a 38 year old white woman, was admitted to the hospital complaining of epigastric pain, chills and icterus. Her liver was enlarged to the iliac crest and was tender. Five years before she had had a cholecystectomy. One year later stricture of the common bile duct developed, and she underwent an operation to transplant the uninvolved duct to the duodenum. The impression was that she was suffering from acute cholangitis. During her stay at the hospital pneumococcic sepsis and terminal acute endocarditis developed. Permission for autopsy was not obtained.

CASE 8.—S. N., a 50 year old white woman, was admitted to the hospital complaining of jaundice of the skin and the scleras coming on after an infection of the upper part of the respiratory tract. She was discharged improved with the diagnosis of toxic hepatitis.

CASE 9.—P. B., a 70 year old white woman, was admitted to the hospital complaining of pain which had been present in the right upper quadrant of the abdomen and the epigastrium for six weeks. One and a half years previously she had had a similar attack with jaundice and clay-colored stools. The liver was definitely enlarged but not tender. Her course was unfavorable; progressive ascites developed, and she died after twenty-two days in the hospital.

CASE 10.—E. S., a 58 year old white woman, was admitted to the hospital for the thirteenth time for jaundice, edema of the ankles and anorexia. On the previous admissions a diagnosis of cirrhosis of the liver had been made. The liver and spleen were not felt.

CASE 15.—A. J., a 35 year old white man, was first admitted to the hospital on Sept. 9, 1937, with symptoms of acute cholecystitis. He improved rapidly without operation and was discharged on September 16. He was readmitted on April 25, 1938, with a history of nausea, vomiting, belching and abdominal pain of five days' duration, which had become progressively worse up to the time of admission. His urine had been dark for two days before admission, and jaundice was noted on the day preceding admission. For the preceding five days his temperature had ranged between 101 and 103 F. On admission he appeared acutely ill. His temperature was 103.4 F. and his pulse rate 120 per minute. There was jaundice of the skin and the scleras. Tenderness and moderate muscular

Comparative Data in Fifteen Cases of Hepatic Manifestations

Case No.	Name	Total Cholesterol, Mg. per 100 Cc.	Free Cholesterol, %*	Phosphorus, Mg. per 100 Cc.	Phosphatase, Units (Bodansky)	Icterus Index	Van den Bergh Test: Direct	Van den Bergh Test: Indirect Units	Urea Nitrogen, Mg. per 100 Cc.	Urobilinogen in Urine	Galactose Tolerance Test	Albumin-Globulin Ratio	Miscellaneous	Diagnosis
1	E. K.	315	35	5.6	21	44	.....	....	140	....	.....	....	.....	Uremia and hepatitis (confirmed by autopsy)
2†	S. B.	321	31	6.7	40.1	Clinically jaundiced	.....	....	43.6	....	.....	....	Uric acid, 12.2 mg. per 100 cc.	Toxemia of pregnancy (patient died within 48 hr.; no autopsy)
3‡	M. B.	127	32	...	13.1	20	Biphasic	3.2	....	1:200	1.26 Gm. excreted in 6 hr.	....	Many firm nodules in enlarged liver, revealed at laparotomy	Carcinoma of liver (no primary source found)
4§	F. K.	290	35	...	5.3	6.7	Negative	0.81	....	....	Normal reaction	....	Normal reaction to dextrose tolerance test	Congenital cysts of liver (revealed at operation)
5‖	D. S.	300	20	...	15	9.8	Delayed	1.08	....	1:10	Negative	....	Takata Ara test, negative; negative reaction for tyrosine in urine	Multiple abscesses of liver (confirmed by autopsy); clinically diabetes mellitus
							Cases in Which Diagnostic Difficulties Were Presented							
6¶	J. A.	394	62	3.9	43	66	Biphasic	12.5	....	1:1	Negative	0.46	Uric acid, 3.7 mg. per 100 cc.; nonprotein nitrogen, 202 mg. per 100 cc.; total protein, 8.5 Gm. per 100 cc.; bromsulfalein test, negative; bile pigments in urine in considerable quantity; sedimentation time, 120 mm. per hr.; fragility test, hemolysis beginning at 0.40 and completed at 0.24	Hepatosplenomegaly of undetermined origin (final diagnosis)
7	L. A.	257	75.5	4	10	64	Immediate	10.9	7.5	....	.....	....	Sugar, 77 mg. per 100 cc.	
8#	S. N.	220	75	...	15	130	Immediate	19	5	At first negative; later 1:10	2 Gm. excreted within 6 hr.	1.34	Bromsulfalein test, 100% retained after 30 min.; total protein, 6.6 Gm. per 100 cc.; fibrinogen, 0.172 Gm. per 100 cc.; bile pigments in urine, 4+; feces, clay colored; sedimentation time, 15 mm. per hr.	Toxic hepatitis

9	P. B.	176	38	3.4	18.6	22	Biphasic	3.54	10	1:40	Negative	1.2	Total protein, 5.23 Gm. per 100 cc.; urobilin and hydrobilirubin in small amounts	Hepatic cirrhosis with superimposed adenomatous changes or carcinoma of the liver
10**	E. S.	218	60	3.6	9.5	20	Biphasic	3.6	9.5	....	Negative	1.35	Total protein, 6.23 Gm. per 100 cc.	Atrophic cirrhosis of the liver
11	A. P.	165	64	...	5.1	167	Immediate	52	....	1:20	6.3 Gm. excreted in 6 hr.	0.54	Fibrinogen, 0.33 Gm. per 100 cc.; total protein, 6.43 Gm. per 100 cc.; tyrosine and leucine constantly absent from urine	Cinchophen poisoning with acute hepatitis
12	V. F.	192	39	...	6.4	193	Immediate	28	3	1:2	.....	....	Sugar, 75 mg. per 100 cc.; bile pigment in considerable quantity in urine	Acute infectious hepatitis
13	H. S.	193	72	2.1	7.5	141	Immediate	37	14.5	Negative	.....	....	Uric acid, 12.1 mg. per 100 cc.; ammonia nitrogen, 1.4 mg. per 100 cc.; creatine, 3.3 mg. per 100 cc.; amino acid nitrogen, 12.4 mg. per 100 cc.; feces, clay colored	Early stages of acute yellow atrophy; renal suppression during last few days of illness (confirmed by autopsy)
14††	E. G.	156	57	3.3	7.7	212	Immediate	36	2.8	Negative	.....	1.3	Amino acid nitrogen, 9.8 mg. per 100 cc.; total protein, 4.8 Gm. per 100 cc.; prothrombin time, 29 min.; fibrinogen, 0.131 Gm. per 100 cc.; feces, clay colored	Acute yellow atrophy (confirmed by autopsy)
15	A. J.	192	43	2.8	8.3	71	Biphasic	....	16.1	....	.....	....	.....	.....

* Free cholesterol × 100 / Total cholesterol

† The cholesterol and the urea nitrogen value indicate a fairly well functioning liver. The icterus index indicates some degree of jaundice. The resultant value for serum phosphatase supports the conclusions regarding the condition of the liver cells and the degree of jaundice (biliary obstruction).

‡ The low cholesterol value and the increased urobilinogen in the urine indicate impaired hepatic function. Only some degree of biliary obstruction was present. When both these factors are considered, the relatively slight increase in serum phosphatase is explained.

§ In this case no chemical evidence of abnormal hepatic function was presented and therefore the normal serum phosphatase value is not of pathologic significance.

‖ The slightly elevated cholesterol value may have been due to diabetes. The moderate increase in phosphatase is characteristic of the unaltered functional state of the liver and the slight degree of biliary obstruction.

¶ Most of the tests point to a fairly well functioning liver. A well functioning liver and biliary obstruction were present; therefore, the serum phosphatase was markedly elevated.

Almost all the tests in cases 7 and 8 indicate a damaged liver. (The percentage of free cholesterol was markedly increased.) Although marked biliary obstruction was present, the phosphatase was only moderately increased because of the hepatic damage.

** The clinical history of cases 9 and 10 suggests previous hepatic damage. With only slight jaundice, the serum phosphatase value is characteristic for the degree of hepatic injury and biliary obstruction.

†† In cases 11, 12, 13 and 14 a similar picture was presented, that is, marked hepatic damage and profound hepatocellular jaundice. In all these cases, the hepatic function was markedly impaired. This accounts for the relatively low value for serum phosphatase even in the presence of marked jaundice.

spasm were present in the right upper quadrant of the abdomen. The clinical diagnosis was exacerbation of chronic cholecystitis, cholelithiasis and obstructive jaundice. He was prepared for operation by intravenous and subcutaneous administrations of dextrose. Operation with the patient under spinal and general anesthesia was performed approximately thirty hours after admission. The liver was found to be enlarged 2 fingerbreadths below the costal margin and was swollen, edematous, yellow-green, smooth and tense. The gallbladder was small, with omentum wrapped around it. It was edematous and hemorrhagic and contained brown-green bile with small pigmented calculi, one of which was impacted in the cystic duct. The common duct was edematous and thick walled, and calculi were palpable in the common hepatic duct.

The common bile duct contained many small calculi, which were removed. The calculi in the hepatic duct could not be dislodged and removed, because of the edema of the duct. Postoperatively the patient was given a transfusion of whole blood, and fluids were injected intravenously. His condition rapidly became poor; the jaundice increased, and he died approximately twenty-five hours after the operation, with the clinical picture of acute hepatic degeneration (liver death). Preoperative determinations are given in the table.

From the table, it is seen that the serum phosphatase values vary from normal levels to 43 units in cases of hepatocellular jaundice. However, if the underlying state of the hepatic parenchyma is considered in addition to the degree of biliary obstruction, a satisfactory explanation suggests itself. In case 6, in which the listed tests of hepatic function indicate fair functioning of the hepatic parenchyma as well as obstruction in the biliary system, the value for serum phosphatase was 43 units. In this case, both equally important factors are present, namely, good functioning of the hepatic parenchyma and an obstruction. This idea is more clearly brought out when cases 13 and 14 are compared with case 1. In the former, the serum phosphatase never rose to more than 7.7 units. In these cases severe intrahepatic (hepatocellular) obstruction was evidenced by the clay-colored stools and the quantity of bile pigments in the blood stream. In the cases of acute yellow atrophy in which autopsy was performed the extremely poor condition of the hepatic parenchyma was revealed (figs. 1, 2, 3 and 4). Case 1 is another instance of hepatocellular obstruction in which autopsy was performed, but in this case the serum phosphatase values were increased to 21 units. It is true that the patient had much less hepatocellular obstruction, but the hepatic parenchyma was much better preserved. In interpreting the significance of the value of 21 units for serum phosphatase, the role of the two factors mentioned must be considered. Here, therefore, are two examples of hepatitis, with different serum phosphatase values. The explanation lies not only in the degree of obstruction but in the underlying pathologic state of the hepatic parenchyma, i. e., the degree of hepatocellular damage. The serum phosphatase values obtained in cases of severe hepatitis and acute yellow atrophy must therefore not be considered negative results or instances in which this test is valueless. The

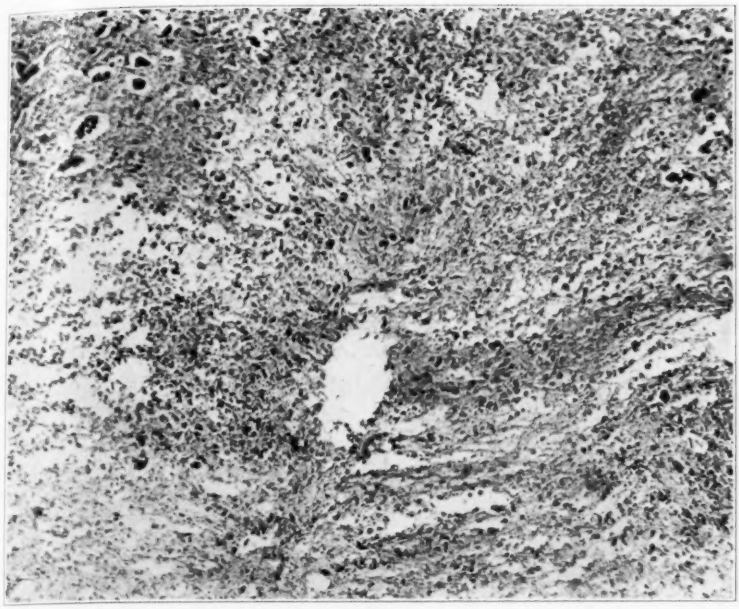

Fig. 1 (× 160).—The architecture of the liver is destroyed. The hepatic parenchyma is represented by pink and lavender amorphous material, containing a diffuse scattering of small round cells, some golden-brown pigment granules, large mononuclear cells, a few plasma cells and an occasional polymorphonuclear leukocyte.

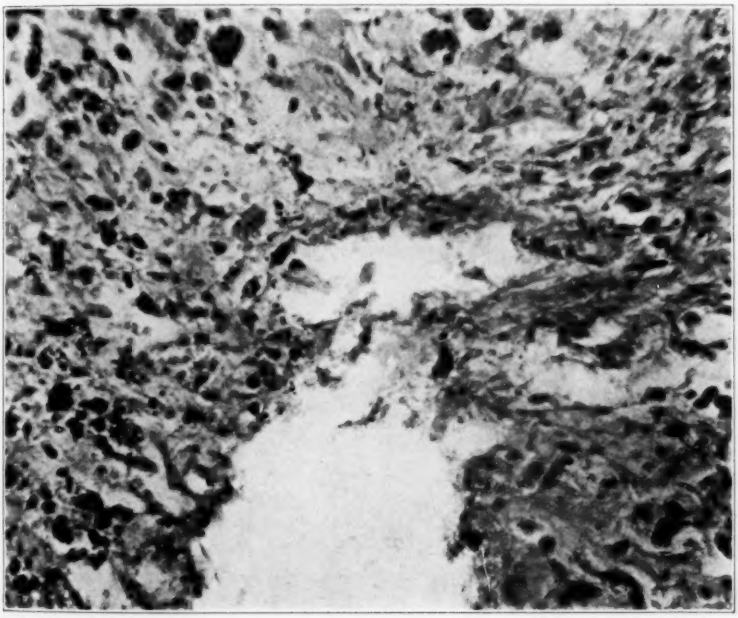

Fig. 2 (× 711).—High power magnification of the section shown in figure 1.

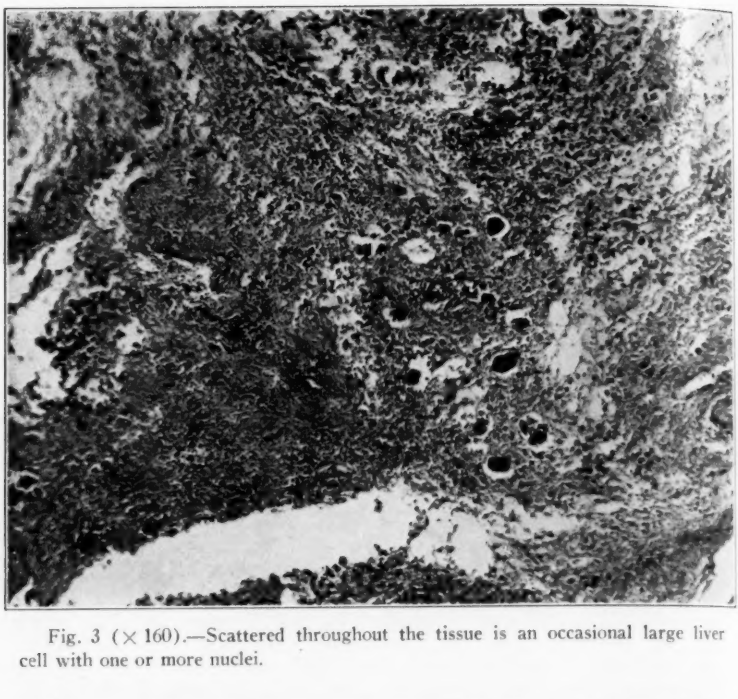

Fig. 3 (× 160).—Scattered throughout the tissue is an occasional large liver cell with one or more nuclei.

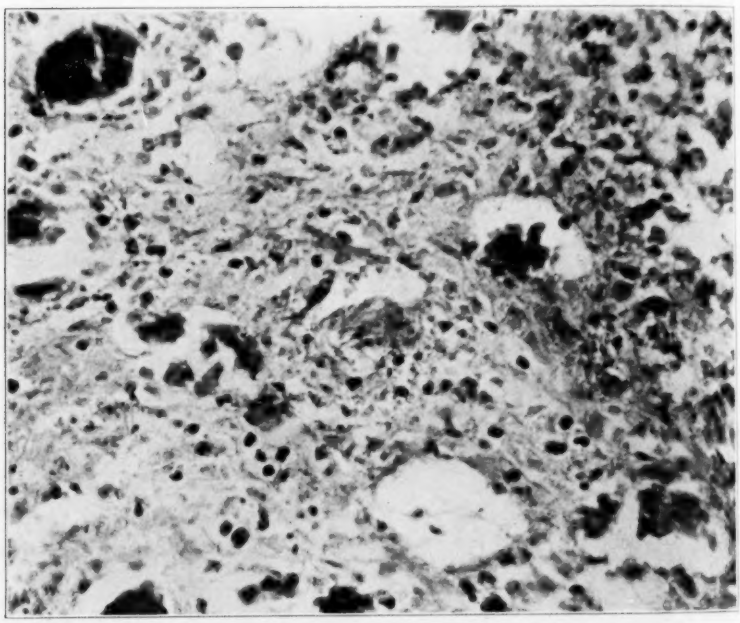

Fig. 4 (× 711).—High power magnification of the section shown in figure 3.

finding of normal serum phosphatase when a definite biliary obstruction is present should be interpreted along with the other laboratory data, especially the total cholesterol and the ratio of free to total cholesterol in arriving at a conclusion regarding the condition of the hepatic parenchyma.

From these statistical studies and the studies of others, especially Cantarow and Nelson,[5] we have found that it is practically impossible to define the different types of jaundice clearly by characteristic values, those of 10 units or above signifying obstructive jaundice and those below 10 units hepatocellular jaundice. This is especially true for the latter condition, in which the values may vary markedly.

From the table one well known fact is brought out clearly, namely, that there is no one adequate test of hepatic function. With the multiplicity of its functions, it is not surprising that the liver can be normal with respect to one function and show abnormalities in another. To interpret each test individually and to correlate its result with the role that the liver plays in the particular function tested will lead to better clinical interpretations and less disappointing results.

It is interesting to correlate the values for serum phosphatase with those for cholesterol as an index of the state of the hepatic parenchyma. In cases of extrahepatic obstruction, the rise in serum phosphatase accompanies the rise in total cholesterol, but when the hepatic parenchyma is damaged the total cholesterol, especially the cholesterol ester, is decreased (Epstein and Greenspan [20]), and the serum phosphatase is normal or only slightly increased even in the presence of an obstruction. This relation and the proper interpretation of serum phosphatase values in clinical cases of jaundice of questionable causation should prove of great value to the clinician and surgeon. The following case is offered as an example:

J. M., a 61 year old white man, was admitted to the hospital with a history of progressive jaundice for the past two weeks. Up to that time he had enjoyed excellent health. He then began to have a poor appetite, felt nauseated and vomited. For three days he had had acholic stools. There was no history of pain. Several days prior to admission his jaundice began to decrease, and his stools became darker. On examination, his liver was palpable in the midline and just to the right of the umbilicus, 3 fingerbreadths below the costal margin. There was no tenderness. Carcinoma of the head of the pancreas with obstructive jaundice being suspected, an exploration was performed two days after his admission. The liver was found to be enlarged to the level of the umbilicus, the right lobe more involved than the left. The liver itself was smooth, slate colored and mottled, with no evidence of palpable masses. There was no evidence of extrabiliary obstruction. No other pathologic condition was found in the abdomen. The patient made an uneventful recovery. The case is therefore one of intrahepatic (hepatocellular) jaundice.

20. Epstein, E. Z., and Greenspan, E. B.: Clinical Significance of the Cholesterol Partition of the Blood Plasma in Hepatic and in Biliary Diseases, Arch. Int. Med. **58**:860 (Nov.) 1936.

LABORATORY DATA

The urine contained bile pigments and small amounts of urobilinogen. Bile pigments were always present in the feces. Blood determinations on several dates were as follows:

Date	Total Cholesterol, Mg. per 100 Cc.	Free Cholesterol, % [21]	Free Cholesterol, Mg. per 100 Cc.	Phosphorus, Mg. per 100 Cc.	Icterus Index	Van den Bergh Test		Urea Nitrogen, Mg. per 100 Cc.	Phosphatase Units (Bodansky)
						Direct	Indirect, Units		
3/20/38	...	..	..	2.9	101	Biphasic	29.2	16.8	6
	(Operation)								
3/23/38	172	44	76	2.4	172	Biphasic	31	....	10.4
3/26/38	158	53	83	...	...	.....	....	23.2	....
4/ 2/38	139	55	76	3.9	91	.....	....	16.5	7.6
4/ 9/38	144	40	58	...	46	.....	....	....	....
4/16/38	188	30	57	3.3	37	.....	....	....	4.8

In this case the cause of jaundice was a problem of differential diagnosis. If it had been a case of extrahepatic obstruction, e. g., carcinoma of the head of the pancreas as suspected, there would have been higher values for total cholesterol and an increase in serum phosphatase. The total cholesterol was at the lower limit of, or slightly below, normality, and there was a marked increase in the percentage of free cholesterol. (The normal values of total cholesterol as determined by the technic employed at the Jewish Hospital of Brooklyn ranges from 160 to 250 mg. per hundred cubic centimeters, the percentage of free cholesterol ranging from 24 to 30 per cent.) In four determinations of serum phosphatase the values did not rise above 10.4 units. These findings are characteristic for hepatocellular disease, which laparotomy proved to be present.

With the concept that serum phosphatase values in hepatic and biliary disorders depend on the functional state of the liver cell and the extent of biliary obstruction, an explanation is now offered for the paradoxic results in three types of cases:

To explain the rise in serum phosphatase in cases of cholecystitis, we refer to the degree of biliary obstruction. To quote Charles H. Mayo [22]: "In cholelithiasis the formation of gallstones is not primary, but there is first biliary tension, next hepatitis or grades of cholangitis, and third, cholecystitis." The slight amount of biliary obstruction from the developing cholangitis is enough to cause a rise in serum phosphatase but not in the icterus index. It has been shown [19] that obstruction of only one seventh, approximately, of the biliary system of a dog will cause more than a tenfold rise in serum phosphatase but no accumulation of the bile pigments.

21. $\frac{\text{Free cholesterol} \times 100}{\text{Total cholesterol}}$.

22. Mayo, C. H.: Unappreciated Hepatic Function, in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol. 2.

In cases of congenital anomalies of the bile ducts in newborn infants, the rise in the icterus index is readily accounted for. Microscopic examination of the livers in such cases reveals the varying degrees of degeneration. Therefore, even though there is an extrahepatic obstruction, the rise in serum phosphatase does not follow, because of the equally important factor, namely, the poor functional state of the liver cell.

In cases of cirrhosis of the liver, the serum phosphatase values vary from normal to 21 units. This may be accounted for by the different degrees of hepatic damage and biliary obstruction that exist in these conditions.

In some cases of extrahepatic obstruction (jaundice caused by a biliary calculus), the values of serum phosphatase often change, depending on the degree of obstruction. In the third type of case, exemplified by case 15 in the table, there evidently is some degree of obstruction. Phosphatase values do not decrease as quickly as the icterus index when the obstruction is released, as proved clinically and experimentally by Armstrong and King.[11] In case 15 the patient had had several attacks of cholangitis previously, and his hepatic parenchyma was probably damaged. This kind of hepatic condition may be the type that predisposes to liver death, as noticed by Graham.[23] The normal or only slightly increased phosphatase value in the presence of a high icterus index, with a clinical story of extrahepatic obstruction, leads one to believe that in this case, although a certain degree of obstruction was present, the poor state of the liver cell prevented more than a slight increase in serum phosphatase and was the underlying cause of the rapid death. Unfortunately permission for autopsy was not obtained.

CONCLUSION

1. In cases of hepatocellular jaundice with obstruction, serum phosphatase values remain normal or increase slightly if the hepatic parenchyma is severely damaged.

2. In cases of hepatocellular jaundice in which obstruction is definitely present and the hepatic parenchyma is in a good functional state, serum phosphatase values are markedly increased. The amount of increase is not clearly characteristic but depends on two factors: (*a*) the functional state of the liver cell and (*b*) the extent of biliary obstruction.

3. Serum phosphatase values are a valuable aid in the differential diagnosis of jaundice. These values must be interpreted along with other hepatic tests to reveal the metabolic and functional state of the hepatic parenchyma and the patency of the biliary channels.

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23. Graham, E. A.: Lowering Mortality After Operations on the Biliary Tract, Illinois M. J. **60**:196, 1931.

Progress in Internal Medicine

INFECTIOUS DISEASES

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In the field of infectious diseases during the past year chemotherapy demanded the most attention. Notable advances in knowledge were made also with respect to the relationship between certain infectious diseases of animals and those of man, to which considerable space has been given in this review. Perhaps the most interesting and important single contribution was the discovery of an enzyme in bacilli found in the soil which actually destroys gram-positive cocci in the test tube and in the animal body.

SULFANILAMIDE AND SULFAPYRIDINE (2-[PARAAMINOBENZENE-SULFONAMIDO]-PYRIDINE) IN THE TREATMENT OF VARIOUS INFECTIONS

Limitation of space permits only a brief résumé of the subject. Lest this become a review of reviews, the reader is referred to a number of general papers and monographs on sulfanilamide and related compounds.[1]

American [2] and British [3] investigators strengthened the view previously held that sulfanilamide exerts its beneficial effect in certain infectious diseases by limiting or preventing the growth of bacteria, thus permitting the body to develop its own immune mechanism to overcome infection. There is no evidence to show that increased action

1. (*a*) Holman, W. L., and Duff, G. L.: Sulfanilamide and Similar Compounds in Chemotherapy, Am. J. M. Sc. **195**:379-416 (March) 1938. (*b*) Whitby, L.: Chemotherapy of Bacterial Infections, Lancet **2**:1095-1103 (Nov. 12) 1938. (*c*) Long, P. H., and Bliss, E. A.: The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds, New York, The Macmillan Company, 1939. (*d*) Mellon, R. R., and Gross, P.: Sulfanilamide Therapy of Bacterial Infections with Special Reference to Diseases Caused by Hemolytic Streptococcus, Pneumococci, Meningococci and Gonococci, Springfield, Ill., Charles C. Thomas, Publisher, 1938. (*e*) Marshall, E. K.: Bacterial Chemotherapy: The Pharmacology of Sulfapyridine, Physiol. Rev. **19**:240-269 (April) 1939.

2. Long, P. H.; Bliss, E. A., and Feinstone, W. H.: Mode of Action, Clinical Use and Toxic Manifestations of Sulfanilamide, J. A. M. A. **112**:115-121 (Jan. 14) 1939.

3. McIntosh, J., and Whitby, L.: The Mode of Action of Drugs of the Sulphonamide Group, Lancet **1**:431-435 (Feb. 25) 1939.

of phagocytic cells, neutralization of toxins or direct effect on the bacterial cell body or capsule takes place. Bacteriostasis is presumably brought about by some interference with the nutrition of the bacterial body which prevents growth or multiplication.

Shaffer [3a] advances evidence to show that sulfanilamide and sulfapyridine exert their therapeutic and toxic effects through oxidation products formed by the action of atmospheric oxygen on these substances under the catalytic influence of respiring tissues or organisms. Other work [3b] shows that pneumococci which become "sulfapyridine-fast" suffer a loss of dehydrogenase activity against certain carbon compounds.

A new compound, sulfapyridine, was introduced [4] in 1938 as an agent more effective than sulfanilamide against pneumococcic infections in mice. It was also supposedly less toxic for the patient than sulfanilamide, but the work of Marshall and co-workers [5] does not support this view. Until more is known about the drug, it should not be used in conditions for which sulfanilamide is effective.

Workers in general who intend to publish observations on the therapeutic effects of any sulfanilamide compounds should read the critical comments of Marshall [6] and of others [7] on the indiscriminate use of newly introduced drugs.

Pneumococcic Infections.—Interest stimulated by reports from England as to the greater effectiveness of sulfapyridine as compared with sulfanilamide against pneumococcic infection in mice has led to widespread use of the drug in the treatment of patients with pneumonia and meningitis, although knowledge of its effectiveness in these composite diseases has not yet been established. In many cases the drug is given on the first appearance of any infection of the respiratory tract. If this custom becomes general, much harm will follow. Uncontrolled and careless use of any valuable drug injures its reputation. Sulfapyridine properly used is valuable in the treatment of patients whose pneumonia or meningitis is caused by the pneumococcus and should be

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3a. Shaffer, P. A.: The Mode of Action of Sulphanilamide, Science **89**:547-550 (June 16) 1939.

3b. MacLeod, C. M.: Metabolism of "Sulfapyridine-Fast" and Parent Strains of Pneumococcus Type I, Proc. Soc. Exper. Biol. & Med. **41**:215-218 (May) 1939.

4. Whitby, L. E. H.: Chemotherapy of Pneumococcic and Other Infections with 2(p-Aminobenzenesulfonamido) Pyridine, Lancet **1**:1210-1211 (May 28) 1938.

5. Marshall, E. K.; Bratton, A. C., and Litchfield, J. T.: The Toxicity and Absorption of 2-Sulfanilamidopyridine and Its Soluble Sodium Salt, Science **88**: 597-599 (Dec. 23) 1938.

6. Marshall, E. K.: An Unfortunate Situation in the Field of Bacterial Chemotherapy, J. A. M. A. **112**:352-353 (Jan. 28) 1939.

7. Bullowa, J. G. M.; Plummer, N., and Finland, M.: Sulfapyridine in the Treatment of Pneumonia, J. A. M. A. **112**:570 (Feb. 11) 1939.

used at present only in cases of infection caused by this bacterium. In my experience it has seemed to be harmful in cases of an atypical form of pneumonia to be described later. It may be argued that it should be used in all cases of acute pulmonary infection as a measure preventive of possible invasion by the pneumococcus, but no evidence is as yet available to support adoption of this plan. It is still of great importance, therefore, to make an etiologic diagnosis of pneumonia in every case before using chemotherapy.

A number of investigators have attempted to explain the mechanism of the beneficial action of the drug. It was thought at first to have some destructive effect on the capsule of the pneumococcus or to reduce the virulence of the organism. Neither of these views has received support. As in the case of other bacteria, bacteriostasis seems to afford the most likely explanation. British observers [8] claim that different strains of pneumococci vary greatly in sensitivity to sulfapyridine and recommend the use of tests to discover whether the pneumococcus to be dealt with in a patient is sensitive or not. Pneumococci, they believe, may become "fast" or resistant to sulfapyridine in the body. Such fastness, resistance or tolerance to drugs or chemicals apparently may be developed in the test tube,[8a] but I have never been convinced of its occurrence in the body. Sulfapyridine, they found, was more effective in animals previously vaccinated against the specific type of Pneumococcus used. Other observers [9] had more success in treating rats when both sulfapyridine and specific immune serum were used than when either was used alone. After infection was well established, serum was more effective than the drug. Sulfapyridine had but little curative effect on lesions in mice caused by pneumococci of types II, III and VIII.[10] Sulfapyridine does not represent the ultimate goal in chemotherapy of pneumococcic infections.[11]

Pneumococcic Pneumonia: Early indications of the effectiveness of sulfapyridine against several types of Pneumococcus led to the hope

8. Maclean, I. H.; Rogers, K. B., and Fleming, A.: M. & B. 693 and Pneumonia, Lancet **1**:562-568 (March 11) 1939.

8a. MacLeod, C. M., and Daddi, G.: A "Sulfapyridine-Fast" Strain of Pneumococcus Type I, Proc. Soc. Exper. Biol. & Med. **41**:69-71 (May) 1939.

9. Kepl, M., and Gunn, F. D.: Sulfapyridine and Serum Therapy in Experimental Lobar Pneumonia of Rats, Proc. Soc. Exper. Biol. & Med. **40**:529-532 (April) 1939.

10. Schmidt, L. H., and Hilles, C.: Further Studies on Therapeutic Properties of Sulfapyridine in Experimental Pneumococcus Infections, Proc. Soc. Exper. Biol. & Med. **40**:611-614 (April) 1939.

11. Bliss, E. A.; Feinstone, W. H.; Garrett, A. W., and Long, P. H.: Sulfapyridine and Sulfanilamide in Experimental Pneumococcal, Meningococcal, Welch Bacillary and Friedländer's Bacillary Infections in Mice, Proc. Soc. Exper. Biol. & Med. **40**:619-621 (April) 1939.

that it would be useful in treating patients with pneumococcic pneumonia, without typing. This hope at present is certainly not justified.

A series of papers published after the one of Evans and Gaisford [12] uniformly show a striking reduction of the duration of illness and of the mortality in cases of pnuemococcic pneumonia following treatment with sulfapyridine. All of them, however, deal with observations made in a single season (1938-1939) and in all a death rate of 4 to 8 per cent is reported.[13] It may be remarked here that other observers noted a death rate of 3.3 per cent in patients treated with specific immune serum alone. According to many physicians, pneumonia in the winter of 1938-1939 was "mild." This suggests only that the prevalence of pneumonia due to Pneumococcus types I, II, III, V and VIII was not as great in certain places as in other years. Furthermore, numerous epidemics of a mild form of pneumonia, apparently not caused by bacteria, occurred in many parts of the country (page 380). Many persons with this form of pneumonia harbored pneumococci in the nasopharynx, as carriers. These pneumococci, which were usually of the higher-numbered types, were found when the sputum was typed. They were often mistaken for the causative agent of the disease, and sulfapyridine was given needlessly. It is highly probable that cases of this form of

12. Evans, G. M., and Gaisford, W. F.: Treatment of Pneumonia with 2-(p-Aminobenzenesulphonamido) Pyridine, Lancet **2**:14-19 (July 2) 1938.

13. (*a*) Dyke, S. C., and Reid, G. C. K.: Treatment of Lobar Pneumonia with M. & B. 693, Lancet **2**:1157-1160 (Nov. 19) 1938. (*b*) Williams, R. B., and Lawson, G. B.: Graphic Evidence of Response with Sulfanilamide in Pneumonia and Pneumococcal Infections, Virginia M. Monthly **65**:727-732 (Dec.) 1938. (*c*) Flippin, H. F.; Lockwood, J. S.; Pepper, D. S., and Schwartz, S.: The Treatment of Pneumococcic Pneumonia with Sulfapyridine, J. A. M. A. **112**:529-534 (Feb. 11) 1939. (*d*) Wilson, A. T.; Spreen, A. H.; Cooper, M. L.; Stevenson, F. E.; Cullem, G. E., and Mitchell, A. G.: Sulfapyridine in Pneumonia, ibid. **112**: 1435-1439 (April 15) 1939. (*e*) Barnett, H. L.; Hartmann, A. F.; Perley, A. M., and Ruhoff, M. B.: The Treatment of Pneumococcic Infections in Infants and Children with Sulfapyridine, ibid. **112**:518-527 (Feb. 11) 1939. (*f*) Sadusk, J. F.: Observations on Sulfanilamide Therapy in Pneumonia and Meningitis Due to Type III Pneumococci, New England J. Med. **219**:787-790 (Nov. 17) 1938. (*g*) Anderson, T. T., and Dowdeswell, R. M.: Treatment of Pneumonia with M. & B. 693, Lancet **1**:252-254 (Feb. 4) 1939. (*h*) Agranat, A. L.; Dreosti, A. O., and Ordman, D.: Treatment of Pneumonia with 2-(p-Aminobenzenesulphonamide) Pyridine (M. & B. 693), ibid. **1**:309-317 (Feb. 11); 380-384 (Feb. 18) 1939. (*i*) Price, A. E., and Myers, G. B.: Treatment of Pneumococcic Pneumonia with Sulfanilamide, J. A. M. A. **112**:1021-1027 (March 18) 1939. (*j*) Hodes, H. L.; Stifler, W. C.; Walker, E.; McCarty, M., and Shirley, R. G.: The Use of Sulfapyridine in Primary Pneumococcic Pneumonia and in Pneumococcic Pneumonia Associated with Measles, J. Pediat. **14**:417-446 (April) 1939. (*k*) Finland, M.; Spring, W. C., Jr.; Lowell, F. C., and Brown, J. W.: Specific Serotherapy and Chemotherapy of the Pneumococcic Pneumonias, Ann. Int. Med. **12**:1816-1829 (May) 1939.

pneumonia were often included in statistics that were reported as showing the beneficial effects of chemotherapy. The presence of pneumococci or other bacteria in the sputum does not always indicate that these organisms have etiologic significance.

According to authoritative opinion,[13k] it seems wisest at present to treat pneumococcic pneumonia with both specific immune serum and sulfapyridine. Generally speaking, when a diagnosis of pneumococcic pneumonia is reasonably certain, and after specimens of blood have been taken for making cultures and cell counts, the patient should be given 2 to 4 Gm. of sulfapyridine while the type of pneumococcus is being determined. When the type is known, specific immune serum and sulfapyridine may then be given together. To patients who for various reasons cannot be given serum the drug may be given alone, and, of course, the reverse applies. The objection to the insolubility of the compound now used may be overcome by use of its sodium salt,[14] but nausea and vomiting still occur, presumably because of an effect of the drug on the central nervous system. While combined use of the serum and drug seems to be advisable now, it is unfortunate for statistical reasons, since the true value of sulfapyridine will be obscured unless the drug is used alone. Before the value of sulfapyridine will finally be known, it will be necessary to use it alone in the treatment of large numbers of patients with pneumococcic pneumonia with particular respect to the type of Pneumococcus, the age of the patient, the presence of other diseases or complications, the presence or absence of bacteremia and the day on which treatment was begun.

Another interesting and important agent capable of attacking pneumococci was discovered by Dubos, whose paper, published during the height of enthusiasm for chemotherapy, received scant attention.[15] He isolated from soil an unidentified spore-bearing bacillus which after it has grown in soil to which suspensions of various gram-positive cocci have been added over a long period forms an enzyme capable of dissolving these cocci. Pneumococci, staphylococci, hemolytic or green-producing streptococci and indifferent streptococci are all susceptible. Besides killing these bacteria when incubated with them in vitro, the bacterial extract injected in minute amounts intraperitoneally into mice protects them against 100,000 fatal doses of pneumococci of types I, II, III, V and VIII. The extract exerts a curative effect also when injected several hours after inoculation of these cocci. It is different from the enzyme previously discovered by Dubos and Avery, which attacks only the polysaccharide capsule of the type III pneumococcus

14. Marshall, E. K., and Long, P. H.: The Intravenous Use of Sodium Sulfapyridine, J. A. M. A. **112**:1671-1675 (April 29) 1939.

15. Dubos, R. J.: Bactericidal Effect of an Extract of a Soil Bacillus on Gram Positive Cocci, Proc. Soc. Exper. Biol. & Med. **40**:311-312 (Feb.) 1939.

and which never had a successful clinical trial. The new extract kills gram-positive cocci but is without effect on gram-negative ones or on gram-negative bacilli. Its effect on infections in man has not yet been reported, but one may predict that it will be useful if it works as well in the patient as it does in mice. If the substance can be standardized and if it is nontoxic, it may even supersede antiserum and sulfapyridine.

Pneumococcic Meningitis: The effectiveness of sulfanilamide and sulfapyridine is more striking in pneumococcic meningitis [16] than in pneumococcic pneumonia, but here again many published reports deal with isolated cases rather than with controlled series of cases. Nevertheless, the number of cases now on record in which recovery followed treatment of this infection, which when untreated is usually regarded as fatal in over 95 per cent of the cases, warrants the use of the drug. Experimental studies in mice showed that 73 per cent of treated animals recovered, as compared with 100 per cent that died in an untreated series.[17]

Finland, Brown and Rauh [18] recommend: frequent complete drainage of spinal fluid; immediate and continuous use of sulfanilamide with sodium bicarbonate; identification of the type of Pneumococcus; intravenous administration of specific antipneumococcus serum until the concentration of immune body in the blood is sufficient; moderate intake of fluid, and intraspinal injection of 5 or 10 cc. of the patient's own serum. The last procedure, recommended as a means of adding to complement, is based on the earlier work of Fothergill in combating meningitis due to the influenza bacillus, but it seems to me to be more theoretic than practical. If anemia results from sulfanilamide, transfusion of blood is advised. Of 10 patients treated, 6 recovered—a noteworthy fact, indeed.

References to many recently published papers on the treatment of pneumococcic meningitis with sulfanilamide may be found in a review by Holman and Duff.[18a]

16. (*a*) Reid, G. C. K., and Dyke, S. C.: Pneumococcic Meningitis Treated with 2-(p-Aminobenzenesulphonamido) Pyridine, Lancet **2**:619-620 (Sept. 10) 1938. (*b*) Neal, J. B.: The Treatment of Acute Infections of the Central Nervous System with Sulfanilamide, J. A. M. A. **111**:1353-1356 (Oct. 8) 1938. (*c*) Hewell, B. A., and Mitchell, A. G.: The Treatment of Pneumococcic Meningitis with Sulfanilamide: Review of Literature and Report of Six Additional Cases, ibid. **112**:1033-1037 (March 18) 1939.

17. Cooper, F. B.; Gross, P., and Lewis, M.: Chemotherapy of Pneumococcal (Type II) Meningitis in the Rat, Proc. Soc. Exper. Biol. & Med. **38**:835-836 (June) 1938.

18. Finland, M.; Brown, J. W., and Rauh, A. E.: Treatment of Pneumococcic Meningitis: A Study of Ten Cases Treated with Sulfanilamide Alone or in Various Combinations with Specific Antipneumococcic Serum and Complement, Including Six Recoveries, New England J. Med. **218**:1033-1044 (June 23) 1938.

In the experience of Hewell and Mitchell [16e] all of 23 children with pneumococcic meningitis treated before 1937 died; with the use of sulfanilamide 4 of 7 patients have recovered. According to their data, there are now reported more than 30 recoveries which followed treatment with sulfanilamide, but in some cases the dose was so small as to render its effectiveness doubtful. At least 9 cases have been reported in which the drug was ineffective; there was bacteremia in 7 of these. These authors review the literature on the subject.

Although no extensive studies of the use of sulfanilamide or sulfapyridine in the treatment of pneumococcic empyema have been reported, it is felt that such treatment is not particularly effective in this condition. Two of my patients had 7 and 17 mg. of sulfapyridine per hundred cubic centimeters of pleural exudate, yet no benefit was apparent. It is curious that the drug should act so well in pneumococcic meningitis and apparently not in empyema.

Ruegsegger's [19] patients with pneumococcic endocarditis all succumbed even though a concentration of 8 to 17 mg. per hundred cubic centimeters of sulfanilamide was present in the blood.

Streptococcic Infections.—According to Chandler and Janeway,[20] growing hemolytic streptococci in dilute sulfanilamide broth does not cause attentuation of these bacteria. Phagocytosis is promoted, but apparently only as a consequence of the toxic effect of the drug on the bacteria and not as a result of any direct effect on phagocytes. Probably a loose union of the drug with the bacterial bodies occurs. The presence of specific antibody greatly increases the bacteriostatic and bactericidal effect of sulfanilamide. Other workers [21] in the same laboratory found that an elevation in electrode potential accompanied sulfanilamide bacteriostasis and that a rapid fall in potential accompanied normal growth. Yet others [22] found that the oxidation-reduction potential was elevated. (See discussion beginning on page 362 and footnotes 3a and 3b.)

Reports have been made of single cases of recovery from meningitis due to the hemolytic streptococcus, after treatment with sulfanilamide. Favorable reports continue to appear about the effect of this therapy on

19. Ruegsegger, J. M.: Pneumococcic Endocarditis, Arch. Int. Med. **62**:388-400 (Sept.) 1938.

20. Chandler, C. A., and Janeway, C. A.: Observations on the Mode of Action of Sulfanilamide in Vitro, Proc. Soc. Exper. Biol. & Med. **40**:179-184 (Feb.) 1939.

21. Fox, C. L.; German, B., and Janeway, C. A.: Effect of Sulfanilamide on Electrode Potential of Hemolytic Streptococcal Cultures, Proc. Soc. Exper. Biol. & Med. **40**:184-189 (Feb.) 1939.

22. Warren, J.; Street, J. A., and Stokinger, H. E.: Influence of Sulfanilamide and Related Compounds upon Oxidation-Reduction Potentials of Hemolytic Streptococcus, Proc. Soc. Exper. Biol. & Med. **40**:208-212 (Feb.) 1939.

erysipelas. Scarlet fever, on the other hand, is not influenced much. In series of cases reported by Sako, Dwan and Platou [23] complications were much less frequent among patients treated with sulfanilamide. Sulfanilamide seemed to be of value in preventing the development of scarlet fever in a number of boys exposed to infection. These authors believe that early intravenous injection of massive doses of serum to combat toxemia together with administration of large doses of sulfanilamide seems to be the best method of treatment for scarlet fever. According to Wesselhoeft and Smith,[24] sulfanilamide does not reduce the toxicity or the duration of scarlet fever. It had no influence in reducing the number of complications unless given over a long period. The drug failed to reduce the number of carriers among convalescent patients.

Coburn and Moore [25] gave sulfanilamide to guinea pigs suffering from abscesses induced by hemolytic streptococci. The abscesses were not sterilized, but when the drug was given either prophylactically or therapeutically cervical adenitis and spontaneous infections were prevented in the treated as compared with the untreated animals. In clinical experiments sulfanilamide given after the onset of incidental streptococcic infection of the throat in patients who had had rheumatic fever did not prevent recrudescence of rheumatic fever; however, when the drug was given to 80 rheumatic children prophylactically, 79 of these children escaped incidental infection with hemolytic streptococci and rheumatic activity. Other work also suggests the prophylactic value of the drug.[26]

Goodman [27] reports 4 cases of a peculiar, previously undescribed form of primary ulcer of skin apparently caused by hemolytic streptococci. Three patients treated with sulfanilamide recovered promptly. Major and Leger [28] report the case of a patient with subacute bacterial

23. Sako, W.; Dwan, P. F., and Platou, E. S.: Sulfanilamide and Serum in the Treatment and Prophylaxis of Scarlet Fever, J. A. M. A. **111**:995-997 (Sept. 10) 1938.

24. Wesselhoeft, C., and Smith, E. C.: The Use of Sulfanilamide in Scarlet Fever, New England J. Med. **219**:947-952 (Dec. 15) 1938.

25. Coburn, A. F., and Moore, L. V.: The Prophylactic Use of Sulfanilamide in Streptococcal Respiratory Infection with Especial Reference to Rheumatic Fever, J. Clin. Investigation **18**:147-155 (Jan.) 1939.

26. Thomas, C. B., and France, R.: A Preliminary Report of the Prophylactic Use of Sulfanilamide in Patients Susceptible to Rheumatic Fever, Bull. Johns Hopkins Hosp. **64**:67-77 (Jan.) 1939. Hoare, E. D.: The Case for Prophylaxis with Sulfanilamide and Sulfapyridine, Lancet **1**:76-79 (Jan. 14) 1939.

27. Goodman, M. H.: Chronic Streptococcic Ulcer of the Skin Unresponsive to Local Therapy but Cured by Sulfanilamide: Report of Two Cases, J. A. M. A. **111**:1427-1431 (Oct. 15) 1938.

28. Major, R. H., and Leger, L. H.: Recovery from Subacute Infectious Endocarditis Following Prontosil Therapy, J. A. M. A. **111**:1919-1920 (Nov. 19) 1938.

endocarditis who was apparently cured by sulfanilamide therapy. The patient died of heart failure twenty-nine days after the temperature had been reduced to normal. The blood became sterile about ten days after the administration of sulfanilamide was begun, and the temperature became normal three days later. At necropsy gram-positive cocci were seen in the leaflets of the aortic valve, but cultures were sterile. I have been informed of several other patients with the disease who were similarly treated but with discouraging results, and in my own experience the temperature of several treated patients was temporarily reduced without other beneficial effects. A similar report is made by Ellis.[29]

Meningococcic Meningitis.—Reports of the effectiveness of sulfanilamide in the treatment of meningococcic infections are uniformly favorable. Numerous papers on the subject are referred to by Whitby.[1b] A paper by Banks [30] is especially valuable. He believes that while combined sulfanilamide and immune serum therapy is valuable, treatment with sulfanilamide alone is just as good. Of 16 patients so treated, 15 recovered. The mortality rate in 59 patients treated with serum and drugs was 11.8 per cent. A similar optimistic report is published by Waghelstein.[31] Among 106 patients the mortality rate in those who were adequately treated was 12 per cent.

Gonococcic Infections.—The effect of sulfanilamide and its compounds on gonorrhea has not been observed long enough to establish the value of these agents as permanently curative or as eliminating gonococci from the entire system. Almost all clinical reports indicate that the effects of treatment are beneficial, especially if treatment is delayed until the primary acute stage has passed.[32] McGregor-

29. Ellis, G. R.: Treatment of Subacute Bacterial Endocarditis with Sulfapyridine, Lancet **2**:1521-1522 (Dec. 31) 1938.

30. Banks, H. S.: Serum and Sulfanilamide in Acute Meningococcal Meningitis, Lancet **2**:7-13 (July 2) 1938.

31. Waghelstein, J. M.: Sulfanilamide in the Treatment of One Hundred Patients with Meningococcic Infection, J. A. M. A. **111**:2172-2174 (Dec. 10) 1938.

32. (*a*) Bowie, F. J. T.: Chemotherapy in Gonorrhea: Preliminary Report on the Use of 2-(p-Aminobenzenesulphonamido) Pyridine, Brit. M. J. **2**:283-284 (Aug. 6) 1938. (*b*) Felke, H.: Chemotherapy of Gonorrhea with Sulfanilamide Compounds Particularly with Diseptal C. (D B 32), Arch. f. Dermat. u. Syph. **178**:45-53 (Aug. 20) 1938. (*c*) McGregor-Robertson, G. J.: Acute Gonorrhea Treated with M. & B. 693: Report on One Hundred Cases, Lancet **2**:1463-1465 (Dec. 24) 1938. (*d*) Cokkinis, A. J., and McElligott, G. L. M.: Sulfanilamide in Gonorrhea: Analysis of Six Hundred and Thirty-Three Cases, ibid. **2**: 355-361 (Aug. 13) 1938. (*e*) Lloyd, V. E.; Erskine, D., and Johnson, A. G.: Chemotherapy of Gonorrhea with M. & B. 693, ibid. **2**:1160-1163 (Nov. 19) 1938. (*f*) Prebble, E. E.: Treatment of Acute Gonorrhea with M. & B. 693, ibid. **2**:1163-

(*Footnote continued on next page*)

Robertson [32e] reports success in treating 100 patients with sulfapyridine and advises against delay in starting treatment. Most observers agree that the greatest good is accomplished by rest in bed during the treatment with the drug. Treatment of ambulatory patients is generally not recommended. Relapse after clinical cure is fairly common. Although certain observers [32g] admit that the mortality from the use of sulfanilamide may be higher than that from gonorrhea alone, they strongly urge the use of the drug. In untreated patients the carrier state may persists for several months; these authors believe it is considerably shortened after treatment with sulfanilamide. Patients with gonorrheal ophthalmia also appeared to be helped by the drug.[33]

Carpenter and his associates [34] present evidence that when sulfanilamide is injected with gonococcus "toxin" into mice it protects the mice from death.

Undulant Fever.—Fifteen or more papers have been published during the year on the use of sulfanilamide in the treatment of brucellosis. Most of them cite favorable effects of the drug in single cases, which in view of the frequent spontaneous remissions of the disease are of little value as evidence. In a number of published charts it seems indicated that the temperature was falling before the drug was given. Neumann [35] reports favorable effects in 20 cases. In 4 cases studied by Welch, Wentworth and Mickle [36] the effect of sulfanilamide in influencing the course of infection was doubtful. They paid much more attention to the effect on the opsonocytophagic index, which seems to me to be of little importance. Bynum [37] was unable to duplicate the satisfactory results obtained by others. The drug, given in adequate doses, did not influence the course in 6 of his cases.

1164 (Nov. 19) 1938, (*g*) Silver, B., and Elliott, M.: The Use of Sulfanilamide in One Thousand Six Hundred and Twenty-Five Cases of Gonorrhea in the Male, J. A. M. A. **112**:723-728 (Feb. 25) 1939. (*h*) Ferguson, C.; Buchholtz, M., and Gromet, R. Y.: Sulfanilamide Therapy in Gonorrhea: Review of Literature and Report of 298 Cases, Am. J. M. Sc. **197**:452-464 (April) 1939.

33. Fernández, L. J., and Fernández, R. F.: Sulfanilamide in Gonorrheal Ophthalmia: Preliminary Report, Am. J. Ophth. **21**:763-766 (July) 1938.

34. Carpenter, C. M.; Hawley, P. L., and Barbour, G. M.: The Protective Action of Sulfanilamide in Mice Against Gonococcal "Toxin," Science **88**:530-531 (Dec. 2) 1938.

35. Neumann, C. Z.: Treatment of Undulant Fever with Prontosil, Brit. M. J. **2**:342-343 (Aug. 13) 1938.

36. Welch, H.; Wentworth, J. A., and Mickle, F. L.: The Use of Sulfanilamide in the Diagnosis and Treatment of Brucellosis, J. A. M. A. **111**:226-237 (July 16) 1938.

37. Bynum, W. T.: Recurrences of Undulant Fever (Brucellosis) Following the Administration of Sulfanilamide, J. A. M. A. **112**:835-836 (March 4) 1939.

Debono [38] used sulfanilamide and the original prontosil (the hydrochloride of 4-sulfamido-2'-4'-diaminoazobenzene) in the treatment of 25 patients suffering from an infection with Brucella melitensis in Malta. In no case could recovery be attributed without doubt to these drugs. He does not feel that chemotherapy, with its element of danger, is justified in cases of brucelliasis. Other physicians in Malta obtained better results. It is obvious that enough information is not as yet at hand to enable one to judge the value of sulfanilamide in the treatment of patients with undulant fever. More valuable information, it seems, could be obtained from controlled experiments in animals, but in the few papers on experimental results published last year [39] it is indicated that only a few animals were used in each investigation—far too few to be of significance. Chinn [39a] treated only 6 infected guinea pigs and decided that the drug is effective in preventing generalized infection. In a later paper [39b] the evidence is more convincing, but positive results were obtained only when the drug was given immediately after infection. Menefee and Poston [39d] showed that sulfanilamide exerts a bacteriostatic action on brucellas inoculated into guinea pigs, especially in the presence of immune bodies.

Miscellaneous Infections.—A number of investigators [40] find sulfanilamide to be of value in the treatment of venereal lymphogranuloma, a disease caused by a filtrable virus, although the permanency of the "cure" is uncertain. Similiar beneficial effects were noted in experimentally infected mice.

There seems to be a difference of opinion as to the effectiveness of sulfanilamide compounds in experimental tuberculosis.[41] According to

38. Debono, J. E.: Treatment of Brucella Melitensis Infection with Prontosil, Brit. M. J. **1**:326-327 (Feb. 18) 1939.

39. (*a*) Chinn, B. D.: In Vitro and in Vivo Effect of Sulfanilamide on Brucella Abortus and Brucella Suis, Proc. Soc. Exper. Biol. & Med. **38**:732-734 (June) 1938; (*b*) The Use of Sulfanilamide in Experimental Brucellosis, J. Infect. Dis. **64**:78-82 (Jan.-Feb.) 1939. (*c*) Wilson, G. S., and Maier, I.: The Sulphanilamide Treatment of Guinea Pigs Infected with Brucella Abortus, Brit. M. J. **1**:8-10 (Jan. 7) 1939. (*d*) Menefee, E. E., and Poston, M. A.: Effects of Sulfanilamide on Brucella Melitensis, var. Melitensis, Abortus and Suis, J. Bact. **37**:269-276 (March) 1939.

40. Shropshear, G.: Sulfanilamide in Treatment of Strictures of the Rectum Caused by Lymphogranuloma Venereum, Illinois M. J. **74**:153-161 (Aug.) 1938. Shaffer, L. W., and Arnold, E.: Lymphogranuloma Venereum, Especially Its Treatment with Sulfanilamide, Arch. f. Dermat. u. Syph. **38**:705-712 (Nov.) 1938. MacCallum, F. O., and Findlay, G. M.: Chemotherapeutic Experiments on Virus of Venereal Lymphogranuloma, Lancet **2**:136 (July 16) 1938. Knight, A. A., and David, V. C.: The Treatment of Venereal Lymphogranuloma with Sulfanilamide, J. A. M. A. **112**:527-529 (Feb. 11) 1939.

41. Greey, P. H.; Baddington, G. D. M., and Little, M. H.: Sulfanilamide and Related Compounds in Experimental Tuberculosis, Proc. Soc. Exper. Biol. &

(*Footnote continued on next page*)

a recent report, sulfanilamide inhibited tuberculosis in guinea pigs, but large doses were needed. No effect was noted in rabbits inoculated intravenously with bovine tubercle bacilli. The drug had little effect on the course of Friedländer bacillus infections in mice [42] or on that of canine filariasis.[43] A few patients with trachoma were apparently aided by sulfanilamide.[44] No effect was noted on tertian malaria,[45] which is disappointing in the face of rather optimistic reports made by others in the previous year. In monkeys experimentally infected with Plasmodium knowlesi Coggeshall [46] observed favorable effects from sulfanilamide, employed both prophylactically and therapeutically. The drug was without effect on infections caused by avian plasmodia.

Thompson and Greenfield [47] studied 1,219 patients with measles and 244 with whooping cough. The patients to whom sulfanilamide was given presented fewer complications, such as otitis media, pneumonia and catarrh. The drug was ineffective in measles.[48] In 4

Med. **40**:418-420 (March) 1939. Ballon, H. C., and Guernon, A.: Effect of Sulfanilamide on the Development of Experimental Tuberculosis in the Guinea Pig, J. Thoracic Surg. **8**:188-194 (Dec.) 1938. Buttle, G. A. H., and Parrish, H. J.: Treatment of Tuberculosis in Guinea Pigs with Sulphanilamide, Brit. M. J. **2**:776-777 (Oct. 15) 1938. Kolmer, J. A.; Raiziss, G. W., and Rule, A.: Sulfanilamide and Derivatives in the Treatment of Experimental Tuberculosis of Guinea Pigs, Proc. Soc. Exper. Biol. & Med. **39**:581-584 (Dec.) 1938. Greey, P. H.; Campbell, H. H., and Culley, A. W.: Effect of Sulfanilamide on Experimental Tuberculosis in the Guinea Pig, ibid. **39**:22-24 (Oct.) 1938. Dietrich, H. F.: Prontosil in Experimental Tuberculosis, Am. Rev. Tuberc. **38**:388-392 (Sept.) 1938.

42. Gross, P.; Cooper, F. B., and Lewis, M.: Sulfanilamide Therapy of Friedländer-Bacillus Infections of Mice, Proc. Soc. Exper. Biol. & Med. **39**: 12-13 (Oct.) 1938.

43. Brown, H. W.: Ineffectiveness of Sulfanilamide in the Treatment of Canine Filariasis, Proc. Soc. Exper. Biol. & Med. **39**:98-100 (Oct.) 1938.

44. Lian, B.: Sulfanilamide in the Treatment of Trachoma, Geneesk. tijdschr. v. Nederl.-Indië **78**:1058-1065 (May 3) 1938. Loe, F.: Sulfanilamide Treatment of Trachoma, J. A. M. A. **111**:1371-1372 (Oct. 8) 1938.

45. Hall, W. E. B.: Sulfanilamide in Tertian Malaria, J. Pharmacol. & Exper. Therap. **63**:353-368 (Aug.) 1938. Faget, G. H.; Palmer, M. R., and Sherwood, R. O.: Unsuccessful Treatment of Malaria with Sulfonamide Compounds, Pub. Health Rep. **53**:1364-1366 (Aug. 5) 1938.

46. Coggeshall, L. T.: Prophylactic and Therapeutic Effect of Sulfonamide Compounds in Experimental Malaria, Proc. Soc. Exper. Biol. & Med. **38**:768-773 (June) 1938; Cure of Plasmodium Knowlesi Malaria in Rhesus Monkeys with Sulfanilamide and Their Susceptibility to Reinfection, Am. J. Trop. Med. **18**:715-722 (Nov.) 1938.

47. Thompson, A. R., and Greenfield, C. R. M.: Chemotherapy in Measles and Whooping Cough: Prophylaxis and Treatment of Complications, Lancet **2**: 991-993 (Oct. 29) 1938.

48. Anderson, T.: Sulfanilamide in the Treatment of Measles, Brit. M. J. **1**:716-718 (April 8) 1939.

patients sulfanilamide seemed to diminish the severity of the eruption as compared with that in 3 untreated patients.

Two patients with actinomycosis improved after treatment with sulfanilamide,[49] but the drug had no effect in a case of rabies in man [50] nor did it change the course of experimental rabies.[51] Experimental plague in rodents was cured with sulfapyridine, but antiplague serum was equally effective.[52] Sulfanilamide was slightly more effective than sulfapyridine in prolonging the life of mice experimentally infected with Bacillus typhosus.[53]

Of 7 patients with smallpox who were treated with sulfanilamide, 4 showed only an evanescent macular eruption as compared with 3 untreated ones, in whom the typical eruption appeared.[54]

PNEUMONIA

Pneumococcic Pneumonia.—A number of studies were made to throw more light on the pathogenesis of pneumococcic pneumonia and on that state known as "diminished resistance," which presumably accounts for the invasion of pathogenic micro-organisms and the development of pneumonia. Robertson [55] summarizes his previous contributions and concludes that pneumococci implanted in the terminal air sacs are dispersed throughout the lobe principally by the edema fluid which spreads to adjacent air passages and through the alveolar pores. He modified his former conclusions as to the importance of macrophages in the process of recovery and now believes that macrophages play only a part in recovery. The cellular reaction may be secondary to some more fundamental change affecting the pneumococci so that they can be disposed of. Recovery from pneumonia, he believes, is due to two factors, one which localizes the infection and the other a local process involving macrophages which enables the body to rid itself

49. Miller, E. M., and Fell, E. H.: Sulfanilamide Therapy in Actinomycosis, J. A. M. A. **112**:731 (Feb. 25) 1939. Hall, W. E. B.: Sulfanilamide and Actinomycosis, ibid. **112**:2190 (May 27) 1939.

50. Hart, B. F., and Evans, E.: Ineffectiveness of Sulfanilamide in Rabies from Vaccinated Dogs, J. A. M. A. **112**:731-732 (Feb. 25) 1939.

51. Gross, P.; Cooper, F. B., and Lewis, M.: Chemotherapy of Experimental Rabies of Rats, Proc. Soc. Exper. Biol. & Med. **40**:649-650 (April) 1939.

52. Schütze, H.: Chemotherapy in Plague Infections, Lancet **1**:266-268 (Feb. 4) 1939.

53. Kolmer, J. A., and Rule, A. M.: Sulfanilamide and Sulfapyridine in Treatment of Experimental B. Typhosus (Eberthella Typhosus) Infection of Mice, Proc. Soc. Exper. Biol. & Med. **40**:615-619 (April) 1939.

54. McCammon, W. D.: Sulfanilamide in the Treatment of Smallpox, J. A. M. A. **112**:1936-1937 (May 13) 1939.

55. Robertson, O. H.: Recent Studies on Experimental Lobar Pneumonia: Pathogenesis, Recovery and Immunity, J. A. M. A. **111**:1432-1437 (Oct. 15) 1938.

of pneumococci. If both processes are active, recovery ensues; if either one or both fail, death follows. After recovery from experimental pneumonia, a high degree of local immunity persists in the lobe involved as long as macrophages are present in the alveoli. Others [55a] found that in infected guinea pigs at the same general period the mononuclear cells increase in number regardless of the outcome.

Nungester and Klepser [56] made experiments with a view to determining what constitutes "lowered resistance." Exposure to cold, deep anesthesia and intoxication with alcohol, respectively, favored aspiration of bacteria-laden mucin placed in the nose. These factors have long been known to favor the onset of pneumonia, and recently more evidence has been added to demonstrate the effect of chilling the body, which causes peripheral vasoconstriction, stasis, anoxemia and impairment of the function of phagocytes in the nasal mucosa.[57] Further studies [58] on the subject tend to show how intoxication with alcohol reduces the resistance to pneumococcic infections. Alcohol apparently has no direct effect on the power of phagocytes to engulf pneumococci but appears to exert some action on capillary walls which prevents egress of leukocytes into the surrounding tissue. Whether the effect is caused by depression of the normal function locally or by disturbance of the central nervous system is uncertain, but the mechanism involved is doubtless one of great importance.

French investigators [59] studied the action of the lungs on bacteria in the blood. Perfused lungs were found to be an effective filter for bacteria added to the blood with which the tests were made.

Frisch [60] watched the behavior of phagocytes and pneumococci in the sputum of patients treated with specific immune serum and with sulfanilamide. Usually clumping of capsulated pneumococci and increased phagocytosis appeared shortly after serum treatment, but

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55a. Fleischer, M. S., and Rich, G. T.: Mononuclear Leukocytes in Blood of Guinea Pigs Experimentally Infected with Pneumococcus, Proc. Soc. Exper. Biol. & Med. **41**:7-10 (May) 1939.

56. Nungester, W. J., and Klepser, R. G.: A Possible Mechanism of Lowered Resistance to Pneumonia, J. Infect. Dis. **63**:94-102 (July-Aug.) 1938.

57. Taylor, H. M., and Dyrenforth, L. Y.: Chilling of the Body Surfaces: Its Relationship to Aural and Sinus Infections, J. A. M. A. **111**:1744-1746 (Nov. 5) 1938.

58. Pickrell, K. L.: The Effect of Alcoholic Intoxication and Ether Anesthesia on Resistance to Pneumococcal Infection, Bull. Johns Hopkins Hosp. **63**: 238-245 (Oct.) 1938.

59. Binet, L., and Jaulmes, C.: Lungs and Microbes, Presse méd. **46**:1281-1282 (Aug. 24) 1938.

60. Frisch, A. W.: Sputum Studies in Lobar Pneumonia: Phagocytosis and the Effect of Serum Therapy, Proc. Soc. Exper. Biol. & Med. **39**:473-477 (Dec.) 1938; Encapsulated Pneumococci in Sputum for Control of Serum Therapy, ibid. **40**:495-496 (March) 1939.

similar changes were often noted in untreated patients. According to Frisch, the test may be used as a method to control serum therapy.

Numerous papers [61] were published during the year on the treatment of pneumonia caused by pneumococci of various types with refined horse serum or rabbit serum. All record favorable results, with the death rate reduced to from 3.3 to 7 per cent. Horn [61,l] observed the effects of serum therapy in 120 patients and reports the death rate reduced to 3.3 per cent, a figure lower than that reported with sulfapyridine therapy. Rabbit serum caused chills in 65 per cent of Loughlin's [61a] 69 patients, but the incidence of serum disease was lower than that following the use of horse serum.

It is often stated that pneumococcic lobar pneumonia in northern Europe is a relatively benign disease as compared with that in the United States. According to Nissen,[61g] however, the mortality rate in Denmark is between 25 and 40 per cent. By giving specific immune serum within the first four days of illness he reduced the death rate to 10 per cent.

Chemotherapy with sulfanilamide and sulfapyridine is discussed on pages 364 to 366. Maclachlan and his associates [62] report beneficial effects

61. (*a*) Loughlin, E. H.; Bennett, R. H., and Spitz, S. H.: The Treatment of Lobar Pneumonia with Rabbit Antipneumococcus Serum, J. A. M. A. **111**: 497-502 (Aug. 6) 1938. (*b*) Baastrup, S.; Transbøl, K., and Nielsen, O. P.: Experiences with Serum Treatment of Lobar Pneumococcic Pneumonias, Ugesk. f. læger **100**:1195-1201 (Oct. 27) 1938. (*c*) Blankenhorn, M. A.: The Present Status of the Serum Therapy of Lobar Pneumonia, J. A. M. A. **111**:1260-1262 (Oct. 1) 1938. (*d*) Nemir, R. L.: Serum Treatment of Pneumonia in Childhood, J. Pediat. **13**:219-235 (Aug.) 1938. (*e*) Plummer, N.: The Use of Serum in the Treatment of the Higher Types of Pneumonia, J. A. M. A. **111**:694-698 (Aug. 20) 1938. (*f*) Andersen, W. T.: Experiences with Serum Treatment of Croupous Pneumonia, Ugesk. f. læger **100**:966-968 (Aug. 25) 1938. (*g*) Nissen, N. I.: Serotherapeutic Studies on Lobar Pneumonia, Especially Treatment with Rabbit Antipneumococcus Serum, Acta med. Scandinav. **98**:231-261, 1939. (*h*) Finland, M., and Brown, J. W.: Specific Treatment of Pneumococcus Type I Pneumonia, Including Use of Horse and Rabbit Antipneumococcus Serums and Sulfanilamide, Am. J. M. Sc. **197**:141-280 (Feb.) 1939. (*i*) Brown, J. W., and Finland, M.: Specific Treatment of Pneumococcus Type II Pneumonia, Including Use of Horse and Rabbit Antipneumococcus Serums and Sulfanilamide, ibid. **197**:369-380 (March) 1939. (*j*) Finland, M., and Brown, J. W.: Specific Treatment of Pneumococcus Type V and Type VII Pneumonias, ibid. **197**:381-390 (March) 1939; (*k*) Treatment of Pneumococcus Type III Pneumonia with Specific Serum and Sulfanilamide, New England J. Med. **220**:365-372 (March 2) 1939. (*l*) Horn, B.: Pneumococcic Lobar Pneumonia: Report of Two Hundred and Forty-Five Cases with Special Reference to Specific Serum Therapy, Ann. Int. Med. **12**:922-931 (Jan.) 1939. (*m*) Rogers, E. S., and Gooch, M. E.: Type I Pneumococcus Pneumonia: Observations from Study of Two Thousand Cases Treated with Specific Serum, New York State J. Med. **38**:1369 (Nov. 1) 1938.

62. Maclachlan, W. W. G.; Johnston, J. M.; Bracken, M. M., and Crum, G. E.: Treatment of Pneumococcic Pneumonia by Hydroxyethylapocupreine, Am. J. M. Sc. **197**:31-39 (Jan.) 1939.

from the treatment of pneumococcic pneumonia with hydroxyethylapocupreine dihydrochloride. The study of Rogers and Gooch [61m] emphasizes the danger of pregnancy as a factor predisposing to pneumonia. The pregnancy rate for patients with type I pneumonia was 6.6 per cent, compared with an estimated rate of 2.2 per cent in a similar age group in the female population. The last four months of pregnancy is the most dangerous time. The same authors show that nonspecific serum has no effect on the course of pneumonia.

Finland and Dublin [63] report studies of 212 cases in which pneumococcic pneumonia complicated pregnancy and the puerperium. About 1 of every 8 women of child-bearing age who had pneumonia were pregnant, 0.63 per cent of all women admitted during pregnancy or parturition had pneumonia, and in 1.2 per cent of women of this age with pneumonia the condition was complicated by pregnancy. Pneumonia accounts for 1 death in every 5,000 deliveries and causes about one half of the maternal deaths from nonobstetric factors. The pneumonia of pregnant women is less often typical as compared with that of nonpregnant women of this age, although the distribution of pneumococcic types among the pregnant women is about the same as among the nonpregnant. Bacteremia was more frequent in pregnant women, and the death rate from pneumonia among them was higher. The death rate from pneumonia was high (45 to 50 per cent) among those who contracted the disease after the sixth month of pregnancy, among those whose pregnancy was terminated during the course of the disease and among those who were not treated with serum. Among 79 patients delivered during pneumonia there were 35 (44 per cent) whose infants were stillborn and 13 whose babies died soon after birth. Labor was often succeeded by shock. All abortions occurred before the seventh month of pregnancy, and none of the babies survived. Of 54 mothers who had pneumonia after delivery at term, 46 had normal babies.

Cecil [64] made an interesting study of the nature of pneumonia encountered in private practice. From time to time one hears that patients with pneumonia can be treated best at home and that the mortality rate in the ones treated at home is lower than in the ones treated in hospitals.[65] This may be true for pneumonia in general but when one compares the different types of pneumonia caused by pneumococci of specific types there is little difference in mortality whether the patients are kept at home or not. A great many statements made concerning

63. Finland, M., and Dublin, T. D.: Pneumococcic Pneumonias Complicating Pregnancy and the Puerperium, J. A. M. A. **112**:1027-1032 (March 18) 1939.

64. Cecil, R. L., and Lawrence, E. A.: Pneumonia in Private Practice: A Study of Nine Hundred and Eleven Cases, J. A. M. A. **111**:1889-1894 (Nov. 19) 1938.

65. Cooper, E. R., and Cecil, R. L.: Pneumonia in Private Practice, Correspondence, J. A. M. A. **112**:168-169 (Jan. 14) 1939.

the supposed mildness of pneumonia in general practice, particularly in country districts, are inaccurate. Unless etiologic diagnoses are made with bacteriologic methods, accurate conclusions cannot be reached.

Hirsch [66] found the average cost of the treatment of a patient with pneumonia to be $167.60. In three quarters of the cases the cost is over $80. The average cost of serum for a patient in a hospital ward is $59. The two major items of expense are hospitalization and the physician's services.

Significance of Pneumococci of the Higher-Numbered Types.—I believe that caution should be used in arriving at an etiologic diagnosis of pneumonia in a patient in whose sputum pneumococci of one of the higher-numbered types are found. Whenever pneumococci of types I, II, III, V, VII, VIII or XIV are present in the sputum of a patient whose illness commenced suddenly with a chill and other signs and symptoms characteristic of lobar pneumonia, one can be almost certain that they are of etiologic significance. But it is often doubtful that pneumococci of any other type are of primary etiologic importance when found in the sputum of a patient with patchy atypical pneumonia, a low leukocyte count and other uncharacteristic signs. Many other bacteria and viruses may cause mild or severe forms of pneumonia, and the pneumococci found in the sputum may be mere saprophytes, which are habitually found in the nasopharyngeal secretions of the patient. If pneumococci are found in the blood stream, they are most likely the cause of the disease, and in many mild infections of the lung pneumococci may, of course, be serious secondary invaders. The decision in many cases is a difficult one to make.

An unusual complication of pneumonia, namely, acute hemorrhagic ulcerative gastroenteritis, was reported under the name of Dieulafoy's disease.[67] It is hardly justifiable to call the condition described by the authors pneumococcic gastroenteritis, since their data do not show that the pneumococcus was the cause of the complication.

Prophylaxis.—Studies on the experimental vaccination of members of the Civilian Conservation Corps have progressed to such a degree that certain facts may now be stated.[68] A soluble pneumococcic

66. Hirsch, J.: A Study of the Economics of Pneumonia: The Costs of Diagnosis and Treatment of Six Hundred and Twenty-Five Cases in New York City, Pub. Health Rep. **53**:2153-2168 (Dec. 9) 1938.

67. Sanford, C. H.; Hughes, J. D., and Weems, J.: Pneumonia Complicated by Acute Pneumococcic Hemorrhagic Ulcerative Gastroenteritis (Dieulafoy's Disease), Arch. Int. Med. **62**:597-603 (Oct.) 1938.

68. Felton, L. D.: Studies on Immunizing Substances in Pneumococci VII: Response in Human Beings to Antigenic Pneumococcus Polysaccharides, Types I and II, Pub. Health Rep. **53**:1855-1877 (Oct. 21) 1938. Ekwurzel, G. M.; Simmons, J. S.; Dublin, L. I., and Felton, L. D.: VIII. Report on Field Tests to Determine the Prophylactic Value of a Pneumococcus Antigen, ibid. **53**:1877-1893 (Oct. 21) 1938.

polysaccharide antigen prepared by Felton was used as an immunizing agent against pneumococci of types I and II. The results are given in the accompanying table.

Although the results are not particularly striking, since no serious outbreaks of pneumonia have occurred there is some indication that the antigen may be effective as an immunizing agent. There is evidence also that the antigen is more effective in adolescents than in persons of more advanced age. The antigen did not lower the incidence of other infections of the respiratory tract. Further studies are under way.

Walsh and Cannon [69] found that nasal instillation of small numbers of pneumococci of type I in rabbits led to fatal septicemia in 70 per cent of them unless they had been vaccinated by dropping killed or autolyzed cultures of type I pneumococci into the nares. Other forms of vaccination, specific or unspecific, were of no value. Since the animals vaccinated intranasally did not have specific antibodies in the

Results of Experimental Immunization with Pneumococcus Types I and II in Civilian Conservation Corps

Vaccinated Group			Control Group		
Persons Studied	Cases of Pneumonia	Deaths	Persons Studied	Cases of Pneumonia	Deaths
3,126	0	0	9,000	8	0
7,500	13	0	7,500	23	2
15,000	18	0	18,000	39	0

blood stream, it seems that the immunity induced was local, involving only the mucous membrane.

Smillie [70] believes the prevention of colds and of overcrowding more important in the control of pneumonia than isolation or quarantine of patients with pneumonia or of those in contact with them. It seems to me, however, that since most persons in contact with pneumococcic pneumonia become temporary carriers of the pneumococcus causing the disease, isolation would at least reduce the number of carriers. This view is shared by Cincinnati internists [71] and by others who previously cited numerous examples of pneumonia apparently contracted by contact with a patient suffering from pneumonia. Colds, they believe, are

69. Walsh, T. E., and Cannon, P. R.: Immunization of the Respiratory Tract: Comparative Study of Antibody Content of Respiratory and Other Tissues Following Active, Passive and Regional Immunization, J. Immunol. **35**:31-46 (July) 1938.

70. Smillie, W. G.: The Prevention of Pneumonia, New York State J. Med. **38**:1485-1489, 1938.

71. Benjamin, J. E.; Ruegsegger, J. M., and Senior, F. A.: Cross Infection in Pneumococcic Pneumonia, J. A. M. A. **112**:1127-1130 (March 25) 1939.

important in predisposing to pneumonia of the homologous type. They urge segregation of patients with colds by the methods employed in wards for patients with contagious diseases.

Other Forms of Pneumonia.—Hadfield [72] makes a further report on the so-called rheumatic pneumonia. While he agrees in general with those who have given previous descriptions, he feels that the sequence of changes has not been given clearly. There is first widespread fibrinous alveolitis, which is followed by infiltration of mononuclear cells. True Aschoff nodes are difficult to identify in lung tissue.

Crämer [73] describes a form of pneumonia caused by inhalation of nitric oxide compound gas. It is characterized by miliary bronchopneumonia.

Chown [74] suggests that the metaplastic reaction in the alveoli and bronchioles in the so-called giant cell pneumonia of infants described by Hecht, Karsner and others may be the result of deficiency of vitamin A.

Dickson [75] publishes more evidence to show that coccidioidomycosis commences as a primary infection of the lungs. In most cases the infection is mild, and recovery is the rule. The disease is usually mistaken for a simple cold or for influenza. Erythema nodosum commonly occurs, even in mild forms. In a few cases the primary attack subsides to be followed later by generalization of the process as a pyemic infection which is highly fatal.

Little attention has been given by Americans to the syndrome called transient hyperergic infiltration of the lung with eosinophilia, described by Löffler in 1931. It may be identical with a peculiar form of "allergic" pneumonia recognized since 1912. Since 1931 numerous Europeans have published reports of cases.[76] The disease is perhaps seldom recognized, because of its mildness. The onset is sudden, with rapidly forming diffuse shadows in the lung, which disappear after three to eight days. Fever is seldom noted, but there may be cough with or without pleural

72. Hadfield, G.: The Rheumatic Lung, Lancet **2**:710-711 (Sept. 24) 1938.

73. Crämer, G.: Pneumonia Caused by Gaseous Nitric Oxide Compounds, Arch. f. Gewerbepath. u. Gewerbehyg. **9**:1-12 (Nov. 12) 1938.

74. Chown, B.: Giant Cell Pneumonia of Infancy as a Manifestation of Vitamin A Deficiency, Am. J. Dis. Child. **57**:489-505 (March) 1939.

75. Dickson, E. C., and Gifford, M. A.: Coccidioides Infection (Coccidioidomycosis): II. The Primary Type of Infection, Arch. Int. Med. **62**:853-871 (Nov.) 1938.

76. Gravesen, P. B.: Transitory Lung Infiltrations with Eosinophilia, Acta med. Scandinav. **96**:523-534, 1938. Leitner, L. J.: Hyperergische, flüchtige, mit Eosinophilie engehende Infiltrate der Lungen bei Tuberkulose und Abortiopneumonien, ibid. **97**:473-507, 1938. Ramsay, H., and Scadding, J. G.: Benign Bronchopulmonary Inflammations Associated with Transient Radiographic Shadows, Quart. J. Med. **32**:79-95 (April) 1939.

pain, and the sputum may be frothy. The cause is unknown, but the condition is thought to be hyperergic in nature, involving the interstitial tissue and the alveoli rather than the bronchi, as in asthma.

A "NEW" INFECTION OF THE RESPIRATORY TRACT

During 1938 a number of cases of a peculiar form of pneumonia in Philadelphia came to my attention.[77] Similar cases were noted in New York, Albany, Boston, Washington, D. C., the state of Georgia, St. Louis, Minneapolis,[78] Chicago, the state of Oregon[79] and England.[80]

The infection started suddenly or gradually, and in the early stage was often regarded as a cold or influenza. There was occasionally a brief period of remission before the temperature rose to high levels. The inflammation spread from the nose or throat to the bronchi, bronchioles and lungs, where a diffuse atypical pneumonia finally developed. The disease was characterized by hoarseness, dyspnea, cyanosis, sweating, stupor, cough with a minimal amount of sputum, high fever and relative bradycardia. In 2 patients signs and symptoms of encephalitis developed. One patient died. The leukocyte count was normal or slightly increased. In a few patients the clinical condition at the height of the illness strongly resembled typhoid fever or psittacosis.

In an attempt to find the cause of the disease Stokes, Kenney and Shaw[81] and Francis and Magill obtained nasopharyngeal washings from most of my patients and inoculated ferrets. From the nasal washings of one patient and from the blood serum of another a filtrable agent was recovered, which caused bacteria-free mononuclear cell pneumonia and encephalitis in ferrets and white mice.

Unfortunately, the virulence of the virus was not maintained in animals, and the virus was lost after ten to fifteen passages, before specific protection tests and other tests could be made to verify its etiologic significance. The virus was either (*a*) the cause of the disease described, (*b*) a commensal or (*c*) a virus found in rodents. The last possibility is not very great, since the virus was found by different investigators in different cities; it was different from other known

77. Reimann, H. A.: An Acute Infection of the Respiratory Tract with Atypical Pneumonia: A Disease Entity Probably Caused by a Filtrable Virus, J. A. M. A. **111**:2377-2384 (Dec. 24) 1938.

78. McKinlay, C. A.: Acute Diffuse Bronchiolitis, Journal-Lancet **59**:90-91 (March) 1939.

79. Miller, F. N., and Hayes, M. G.: Bronchopneumonia of Mild Severity at the University of Oregon, Northwest Med. **38**:12-14 (Jan.) 1939.

80. Andrewes, C. H.: Epidemic Influenza, Lancet **1**:589-591 (March 11) 1939.

81. Stokes, J.; Kenney, A. S., and Shaw, D. R.: A New Filtrable Agent Associated with Respiratory Infections, Tr. Coll. Physicians Philadelphia **6**:329-333 (Feb.) 1939.

viruses; it died out during passage (if of animal origin it probably would have persisted), and it was obtained from the nasal washings and blood of 2 members of the same family.

The question arose whether the infection is a "new" disease or whether it is a member of a group of atypical infections heretofore called colds, bronchopneumonia or capillary bronchiolitis. I regarded it rather as a newly recognized severe form of an otherwise mild and perhaps commonly encountered infection of the respiratory tract. The infection as described has many features in common with pneumonia caused by other filtrable viruses, such as the pneumonia of psittacosis, vaccinia, measles or influenza. One wonders whether the epidemic disease in the Faroe Islands described by Rasmussen [82] as a psittacosis-like disease is not the same as that described here. Stahel [83] studied an explosive outbreak of an infectious disease in a Swiss regiment. Of 930 soldiers, 108 had catarrhal symptoms with profuse perspiration, myalgia and diphasic fever. Because 6 of the affected soldiers had persistent headache, stiffness of the neck and myalgia, Stahel regarded the epidemic as one of poliomyelitis in spite of a morbidity rate of 14 per cent and no sequels. From the brief description given it seems more likely that it was predominantly an infection of the respiratory tract which involved the central nervous system in a few cases.

A virus obtained from other patients with infection of the respiratory tract which caused meningitis and pneumonitis in animals was studied by Francis and Magill.[84]

In view of the fact that experimental animals, especially white mice, guinea pigs and rabbits, harbor numerous native viruses that are filtrable, it is necessary to use caution in interpreting a disease observed to occur in such animals after injection of materials obtained from human patients, as signifying the transfer of disease from these patients. Gordon, Freeman and Clampit [85] reported the discovery in mice of a filtrable agent which causes pneumonia. The disease is easily confused with that caused by the inoculation of mice with the virus of epidemic influenza except for the absence of metaplastic replacement of the bronchiolar epithelium. Further differentiating it from influenza is a focal necrosis

82. Rasmussen, R. L.: Er primer epidemisk alveolopneumoni og psittacosis samme sygdoms? Ugesk. f. læger **100**:989-998 (Sept. 1) 1938.

83. Stahel, H.: Die Poliomyelitis Epidemie, Schweiz. med. Wchnschr. **68**:86-91, 1938. Epidemic of Poliomyelitis in a Regiment, Foreign Letters, J. A. M. A. **111**: 74 (July 2) 1938.

84. Francis, T., and Magill, T. P.: An Unidentified Virus Producing Meningitis and Pneumonitis in Experimental Animals, J. Exper. Med. **68**:147-160 (Aug.) 1938.

85. Gordon, F. B.; Freeman, G., and Clampit, J. M.: A Pneumonia-Producing Filtrable Agent from Stock Mice, Proc. Soc. Exper. Biol. & Med. **39**:450-451 (Dec.) 1938.

of the liver which occurs. Horsfall and Hahn [86] likewise report a virus from normal mice capable of inciting pneumonitis when inoculated intranasally into normal mice. Their virus, however, was not the same as that described by the aforementioned observers or as mine; it was strictly pneumonotropic in mice, it was nonpathogenic when inoculated intraperitoneally or intracerebrally, and it was not virulent for ferrets.

At the May meeting of the Association of American Physicians Stokes and I gave further evidence to support the view that the disease I described in 1938 was the severe form of a widely distributed infection of the respiratory tract. In February and March of 1939 a widespread epidemic broke out in Philadelphia. Nearly 50 per cent of a group of 800 persons comprised of nurses, students and interns at Jefferson Hospital were ill during this time. Of this group, 78 per cent were mildly ill and ambulatory, 15 per cent were moderately ill and confined to bed, and 7 per cent had the severe form of the disease, with pneumonia. None died. No definite evidence of the isolation of a virus was found when nasopharyngeal washings were inoculated into ferrets by Stokes and Shaw. The virus of epidemic influenza, or evidence of its presence, was not obtained.

A similar epidemic was noted in Ithaca, N. Y., among university students. The observers [87] preferred to call the disease acute interstitial pneumonitis, but no necropsy material was available to support this description. I had previously mentioned the term "virus pneumonia," but this term also is not desirable unless a virus can be proved to cause the disease. Furthermore, in only a small percentage of those ill were the lungs involved. Since an etiologic diagnosis is preferable to an anatomic one, it is best not to give the entity a definite name until its cause can be found. It is perhaps better, also, to regard it as a newly described disease rather than a new disease.

Goodpasture and his co-workers [88] observed a hitherto undescribed "virus pneumonia" in 5 infants. The virus invasion appeared to be secondary to measles and whooping cough and seemed to pave the way for bacterial invasion of the lung. Animals could not be infected by experimental inoculation of lung tissue. The virus was not that of herpes simplex nor that of the so-called inclusion disease of infants. The pulmonary lesions showed characteristic intranuclear inclusions, present almost exclusively in the epithelial cells of the trachea, bronchi

86. Horsfall, F. L., and Hahn, R. G.: A Pneumonia Virus of Swiss Mice, Proc. Soc. Exper. Biol. & Med. **40**:684-686 (April) 1939.

87. Smiley, D. F.; Showacre, E. C.; Lee, W. F., and Ferris, H. W.: Acute Interstitial Pneumonitis: A New Disease Entity, J. A. M. A. **112**:1901-1904 (May 13) 1939.

88. Goodpasture, E. W.; Auerbach, S. H.; Swanson, H. S., and Cotter, E. F.: Virus Pneumonia of Infants Secondary to Epidemic Infections, Am. J. Dis. Child. **57**:997-1011 (May) 1939.

and alveoli. Epithelial necrosis and ulceration of the tracheal and bronchial mucosa and interstitial pneumonia followed.

INFLUENZA

According to Francis and Magill,[89] there were marked differences and striking similarities in antigenic characteristics among 24 strains of the virus of epidemic influenza. A rough grouping of strains is possible, but the characteristics of one group merge with those of another. The differences which were found, they believe, scarcely warrant the designation of types. The conclusions of Smith and Andrewes [90] on the same subject, published in the same journal, differ somewhat from those of Francis and Magill. To account for the divergent results, the English investigators suggest that the strains studied by Francis and Magill all fall into a group which in England is regarded as "intermediate." Smith and Andrewes classify strains of influenza virus into three main categories, namely, highly specific, relatively nonspecific and intermediate strains. It is obvious that many strains do exist, which is a consideration of importance for epidemiologic and prophylactic reasons. This multiplicity may account for second attacks, the latter being due to strains antigenically dissimilar to those causing the first attack. It is still unknown whether the various types of strains are of stable antigenic constitution or whether significant variation occurs. Several apparently different strains may be encountered in a single epidemic.

Francis and Stuart-Harris [91] made studies similar to those reported by Straub in 1937 and found the virus of influenza to cause a specific injury of the nasal mucosa in ferrets. Study of the process of repair showed on about the sixth or eighth day an abnormal type of epithelium that was resistant to further virus infection and to injury by zinc sulfate. After twenty-one days the membrane was again normal in type and susceptible to injury. The destruction of the membrane in the early period seems to permit invasion by pathogenic bacteria. Stuart-Harris [92] caused a strain of influenza virus to become neurotropic in young mice

89. Magill, T. P., and Francis, T.: Antigenic Differences in Strains of Epidemic Influenza Virus, Brit. J. Exper. Path. **19**:273-284 (Oct.) 1938. Francis, T. and Magill, T. P.: Cross-Immunization Tests in Mice, ibid. **19**:284-292 (Oct.) 1938.

90. Smith, W., and Andrewes, C. H.: Serologic Races of Influenza Virus, Brit. J. Exper. Path. **19**:293-314 (Oct.) 1938.

91. Francis, T., and Stuart-Harris, C. H.: Studies on the Nasal Histology of Epidemic Influenza Virus in the Ferret, J. Exper. Med. **68**:813-830 (Dec.) 1938.

92. Stuart-Harris, C. H.: A Neurotropic Strain of Human Influenza Virus, Lancet **1**:497-499 (March 4) 1939.

by passage on chorio-allantoic membrane. Leish [93] calls attention to the remarkable tissue specificity of influenza virus. In tissue culture experiments the virus grew best in lungs of embryos. The more embryonic the tissue, however, the wider the range of organs in which growth was possible.

At the meeting of the American College of Physicians in the spring of 1938 Goodpasture reported the culture of influenza virus in chick embryos. Vaccine made from such cultures may eventually prove practical for the prevention of influenza.

Shope [94] suggests that lungworm larvae from pigs which harbor influenza virus may carry the virus to earthworms, which in turn are eaten by other pigs, which may then acquire the infection in a subclinical form. Influenza may be provoked in these hogs by injecting Haemophilus influenzae suis intramuscularly or by nonspecific measures, such as injecting calcium chloride solution intrapleurally.

Magill and Francis [95] demonstrated a flocculation reaction when serums of patients convalescent from influenza were mixed with suspensions of lung tissue from mice infected with influenza virus. It was not definitely established whether the reaction was specific for the virus of influenza or not.

ANIMALS AS HOSTS OF INFECTIOUS AGENTS OF MAN

The importance of animals as reservoirs of infections which may spread to man is receiving an increasing amount of attention. Although a few of the more obvious infections which involve both man and animals have long been known, such as glanders, anthrax, foot and mouth disease, rabies, plague, tuberculosis and smallpox, other infections, less striking in their manifestations or in their mortality rate, have been dealt with only in recent years. They include tularemia, undulant fever, the typhus–spotted fever group of rickettsial diseases, those caused by filtrable viruses, such as choriomeningitis, "equine" encephalomyelitis, jungle yellow fever, influenza, swineherd's disease, psittacosis and louping ill, and the spirochetal group with rat-bite fever, relapsing fever and Weil's disease.

To emphasize the importance of this group of diseases involving both man and animals I have gathered together the following information as indicative of the advances in knowledge made in this direction in 1938.

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93. Tissue Specificity of Influenza Virus, Foreign Letters, J. A. M. A. **112:** 1615 (April 22) 1939.

94. Shope, R. E.: An Intermediate Host for the Swine Influenza Virus, Science **89**:441-442 (May 12) 1939.

95. Magill, T. P., and Francis, T.: A Flocculation Phenomenon with Human Sera and Suspensions of the Virus of Epidemic Influenza, Proc. Soc. Exper. Biol. & Med. **39**:81-84 (Oct.) 1938.

Lymphocytic Choriomeningitis.—Armstrong and Sweet [96] report 2 cases of lymphocytic choriomeningitis from Washington, D. C. Gray house mice trapped in the homes of the patients were found to harbor the virus which causes the disease. The virus was not present in mice caught elsewhere. Mice were, therefore, incriminated as a reservoir of the disease from which man is infected. It seems to me, however, that, as in the controversey on human influenza and hog influenza, it is not possible to tell whether the mice did not contract the infection from the human patients.

Coggeshall [97] proved experimentally that mosquitoes may transmit the virus of lymphocytic choriomeningitis from infected monkeys or guinea pigs to normal ones. Mosquitoes are infectious as early as the fourth day and as late as the fifteenth day after feeding on a sick animal.

Howard [98] points out how important it is to make an etiologic diagnosis in cases of this disease, since, she believes, other agents may give rise to similar signs and symptoms.

Encephalomyelitis.—In 1931 Meyer, Haring and Howitt reported the discovery of a virus which caused an outbreak of encephalomyelitis among horses and mules in California. Because of the occurrence of the disease in these animals it was called equine encephalomyelitis. Later Meyer suggested that human beings may contract the disease from horses and reported 3 cases in which this may have occurred. In 1936 an epidemic among horses in Montana was recognized.[99]

In 1935 the disease was noted among horses in the eastern part of the United States, but the virus isolated differed somewhat serologically from that causing the western variety of this disease. The discovery of the disease in different parts of the country brings up the question raised before concerning tularemia, undulant fever and the eastern variety of Rocky Mountain spotted fever—i. e., whether it is a new disease and whether it is spreading. It is my belief that none of these are new diseases in the sense of never having existed before. It is more likely that they appear sporadically in unrecognized form or periodically in wavelike epidemics to subside to unimportance in interepidemic periods. They are diagnosed only after some one shows how to do it or after the etiologic agent is discovered.

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96. Armstrong, C., and Sweet, L. K.: Lymphocytic Choriomeningitis: Report of Two Cases, with Recovery of the Virus from Gray Mice (Mus Musculus) Trapped in the Two Infected Households, Pub. Health Rep. **54**:673-684 (April 28) 1939.

97. Coggeshall, L. T.: The Transmission of Lymphocytic Choriomeningitis by Mosquitoes, Science **89**:515-516 (June 2) 1939.

98. Howard, M. E.: Lymphocytic Choriomeningitis: A Discussion of Its Diagnosis in Man, J. Infect. Dis. **64**:66-77 (Jan.-Feb.) 1939.

99. Cox, H. R.; Philip, C. B.; Marsh, H., and Kilpatrick, J. W.: Observations Incident to an Outbreak of Equine Encephalomyelitis in the Bitterroot Valley of Western Montana, J. Am. Vet. M. A. **93**:225-232 (Oct.) 1938.

In 1938 striking new facts were discovered concerning "equine" encephalitis. In September Fothergill and his associates [100] and Webster and Wright [101] reported that they had isolated the virus of the eastern disease from human patients, fulfilling Meyer's prediction of 1933. Schoening and his associates [102] then succeeded in infecting horses with the virus obtained from one of these patients. The virus caused disease when inoculated into normal horses and in those previously rendered immune to the western variety of virus but not in those immunized against the homologous eastern strain. The virus is specific and is apparently not related to the virus of lymphocytic choriomeningitis, the St. Louis type of encephalitis or von Economo's encephalitis lethargica.

In November and December several other clinical reports were published.[103] Ecklund and Blumstein [103a] in Minnesota and Howitt [103b] in California reported infections of the western variety in man. A detailed clinical and pathologic description of the disease as observed in 4 cases was published by a group in Boston.[103c] It appears that an outbreak of encephalomyelitis occurred in horses in the New England states in August 1938. More than 200 horses died. At the same time encephalitis developed in numerous persons, and 30 or more were studied. The mortality rate among horses was 90 per cent. The death rate for the patients was high (25 of 38 died) in contrast with that for patients with encephalitis lethargica, but no doubt many mild attacks went unrecognized.

A surprising report came in November from Tyzzer, Sellards and Bennett,[104] who discovered the virus of the eastern variety of "equine"

100. Fothergill, L. D.; Dingle, J. H.; Farber, S., and Connerley, M. L.: Human Encephalomyelitis Caused by the Virus of the Eastern Variety of Equine Encephalomyelitis, New England J. Med. **219**:411 (Sept. 22) 1938.

101. Webster, L. T., and Wright, F. H.: Recovery of Eastern Equine Encephalomyelitis Virus from Brain Tissue of Human Cases of Encephalitis in Massachusetts, Science **88**:305-306 (Sept. 30) 1938.

102. Schoening, H. W.; Giltner, L. T., and Shahan, M. S.: Equine Encephalomyelitis Produced by Inoculation of Human Encephalitis Virus, Science **88**:409-410 (Oct. 28) 1938.

103. (*a*) Ecklund, C. M., and Blumstein, A.: The Relation of Human Encephalitis to Encephalomyelitis in Horses, J. A. M. A. **111**:1734-1735 (Nov. 5) 1938. (*b*) Howitt, B.: Recovery of the Virus of Equine Encephalomyelitis from the Brain of a Child, Science **88**:455-456 (Nov. 11) 1938. (*c*) Wesselhoeft, C.; Smith, E. C., and Branch, C. F.: Human Encephalitis: Eight Fatal Cases, with Four Due to the Virus of Equine Encephalitis, J. A. M. A. **111**:1735-1741 (Nov. 5) 1938. (*d*) Feemster, R. F.: Outbreak of Encephalitis in Man Due to the Eastern Virus of Equine Encephalomyelitis, Am. J. Pub. Health **28**:1403-1410 (Dec.) 1938.

104. Tyzzer, E. E.; Sellards, A. W., and Bennett, B. L.: The Occurrence in Nature of "Equine Encephalomyelitis" in the Ring-Necked Pheasant, Science **88**: 505-506 (Nov. 25) 1938.

encephalomyelitis in ring-necked pheasants. Numbers of these birds had been found paralyzed in Connecticut and died before shipment to the laboratory. It was suggested that the adjective "equine" might be a misnomer; the horse may simply be another species susceptible to an infection which occurs naturally in wild life. Other wild and domestic fowl are known to be susceptible to the virus, and migratory birds are implicated as a possible permanent source of infection. During the epidemic among horses in August pigeon breeders noted an unusual fatal disease among their birds. From one of the dead birds Fothergill and Dingle [105] isolated the virus.

The ease with which mice can be infected suggests that rodents may be a source of the disease, as they are of typhus, spotted fever, plague and tularemia. Numerous investigators have suggested that insects, particularly mosquitoes, are vectors of the infection. These problems provide experimental work for the next decade or two.

A somewhat similar disease was reported in Canada and in Venezuela. Beck and Wyckoff [106] studied a strain sent from South America and found it to produce a disease somewhat similar to the eastern variety of encephalomyelitis, yet immunologically it is different from both the eastern and the western variety of the virus, especially from the latter.

St. Louis Encephalitis.—In further epidemiologic studies on the outbreaks of encephalitis in St. Louis Casey and Broun [107] noted a concentration of cases in vicinities of sewage and refuse dumps, streams, ponds and overgrown weeds. The outbreaks had no epidemiologic features suggesting an association with bad housing, crowding or cold weather, and there were no multiple "house" cases, but every observed feature suggests a similarity to such mosquito-borne diseases as yellow fever, malaria and perhaps equine encephalitis. The outbreaks had no connection with the water supply, food supply or milk supply. They involved the same widely separated areas in two different years and occurred only in the warm months.

Armstrong [108] inquired into the prevalence of encephalitis in warm months. He found that the nonspecific protection resulting from the irritation of instilling cultures of nonpathogenic bacteria into the nares was sufficient to render mice resistant to subsequent intranasal inoculation with the virus of St. Louis encephalitis. Mild infections of the

105. Fothergill, L. D., and Dingle, J. H.: A Fatal Disease of Pigeons Caused by the Virus of the Eastern Variety of Equine Encephalomyelitis, Science **88**:549-550 (Dec. 9) 1938.

106. Beck, C. E., and Wyckoff, R. W. G.: Venezuelan Equine Encephalomyelitis, Science **88**:530 (Dec. 2) 1938.

107. Casey, A. E., and Broun, G. O.: Epidemiology of Saint Louis Encephalitis, Science **88**:450-451 (Nov. 11) 1938.

108. Armstrong, C.: Studies in the Mechanism of Experimental Intranasal Injections in Mice, Pub. Health Rep. **53**:2004-2012 (Nov. 11) 1938.

respiratory tract which affect so large a proportion of the population in the winter may have a similar nonspecific preventive effect during the cold months.

Toxoplasmosis.—Encephalitis caused by Toxoplasma, a protozoan parasite of various mammals and birds, has been reported in several infants recently. Wolf, Cowen and Paige [109] report the transmission of the infection to rabbits and mice. They suggest that human toxoplasmosis may take on clinical forms aside from encephalitis, as suggested by pathologic studies in a report from France.

De Morsier [110] raises the question, often discussed before, of the relation of herpes simplex to encephalitis. There has been a good deal of uncertainty as to whether the two when they occur at the same time are caused by the same virus or not. This French observer believes that a relationship exists but makes no mention of attempts to prove his point with experimental studies. Similar uncertainty obtains in regard to the encephalitis of mumps,[111] that of vaccinia, postvaccinal encephalitis, postinfluenzal encephalitis and other encephalitides. Recently I noted encephalitic symptoms in 2 patients with a severe infection of the respiratory tract. A virus, presumably the cause of the disease, was isolated from one of the patients. The virus caused encephalitis and pneumonia in mice and guinea pigs. This observation strengthens the view that numerous viruses may have the capacity to affect the nervous system in addition to the tissues and organs which they usually involve.

Acute Anterior Poliomyelitis.—Frauchiger and Messerli,[112] of Switzerland, report what they believe to be acute anterior poliomyelitis in a heifer and in hogs. The symptoms, they state, were typical of the disease in man, but no other cattle and no human beings were affected at the time. One animal was killed, and microscopic examination revealed changes in the lumbosacral portion of the spinal cord identical with those found in man. Whether the virus which caused the disease was identical with that which causes disease in man is not certain, but

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109. Wolf, A.; Cowen, D., and Paige, B.: Human Toxoplasmosis: Occurrence in Infants as an Encephalomyelitis; Verification by Transmission to Animals, Science **89**:226-227 (March 10) 1939.

110. de Morsier, G.: Herpetic Encephalitides: Apoplectic Form, Convulsive and Hallucinatory Form; Contagion by Herpetic Virus, Presse méd. **46**:1611 (Nov. 2) 1938.

111. Fuhrmann, K. G.: Nervous Complications in Epidemic Parotitis: Meningoradiculitis Basalis Parotidea, Hospitalstid. **81**:159-168 (Feb. 8) 1938. Finkelstein, H.: Meningo-Encephalitis in Mumps, J. A. M. A. **111**:17-19 (July 2) 1938.

112. Case of Spontaneous Poliomyelitis in an Animal, Foreign Letters, J. A. M. A. **111**:74 (July 2) 1938. Frauchiger, E., and Messerli, W.: Further Cases of Spontaneous Poliomyelitis in Domestic Animals (Hogs), Schweiz. med. Wchnschr. **69**:74 (Jan. 28) 1939.

the possibility is highly important. To test the theory further, Frauchiger and Hofmann [113] inoculated 3 heifers with virus from a human patient with poliomyelitis. Each animal became ill with suggestive symptoms, and the spinal fluid gave evidence of infection. Histologic studies were not reported.

These reports led Lumsden [114] to suggest the possibility mentioned before but never supported, namely, that the stable fly may be a carrier of the virus of this disease. The epidemiology of poliomyelitis is similar to that of other insect-borne diseases, such as typhoid fever, malaria and yellow fever.

In 1937 a sudden epidemic believed to have been poliomyelitis broke out in a Swiss regiment.[83] In a period of twelve days in July, 6 of 930 soldiers were taken ill with meningeal and myelitic symptoms, 16 with meningeal symptoms alone and 108 with catarrhal symptoms. There was difficulty in differentiating the disease from influenza. In reading this brief report one wonders whether this disease actually was acute anterior poliomyelitis. The morbidity rate of 14 per cent and the recovery without sequels in most of the cases do not conform with the usual description of acute anterior poliomyelitis, and no authentic cases of poliomyelitis were noted among the civil population at the same time. Furthermore, the great predominance (83 per cent) of infections of the respiratory tract, as indicated by catarrhal symptoms with profuse sweating, suggests that some pneumonotropic virus may have been operative which in an occasional patient attacked the nervous system, similar to the cases of atypical pneumonia described elsewhere in this review.

Toomey [115] doubts whether many of the recorded cases of second attacks of poliomyelitis can be accepted as such. Other infections which follow an attack of poliomyelitis may cause further harm and aggravate the symptoms already present. Draper and Dupertius [116] attempt to show a relationship between constitutional factors and susceptibility to poliomyelitis. Persons whose body measurements conform to a certain form seem to be more susceptible to the disease than others. In susceptible persons a tendency to overgrowth and retarded development was often noted. Particularly noticeable were a mongoloid type of eye and fetal and infant-like retardation of the eye-nose zone.

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113. Frauchiger, E., and Hofmann, W.: Experimental Transmission of Poliomyelitis to Cattle, Schweiz. med. Wchnschr. **68**:1140-1141 (Oct. 8) 1938.

114. The Stable Fly as a Possible Carrier of the Virus of Infantile Paralysis. Science News, Science (supp.) **88**:10-11 (Oct. 14) 1938.

115. Toomey, J. A.: Second Attacks of Poliomyelitis, Am. J. Dis. Child. **59**: 969-974 (Nov.) 1938.

116. Draper, G., and Dupertius, C. W.: The Nature of the Human Factor in Infantile Paralysis: I. Peculiarities of Growth and Development; II. Relation of Age to Maturing Achievement and the Disease Picture, J. Clin. Investigation **18**:87-100 (Jan.) 1939.

Typhus Fever.—The infectious agent of typhus fever was found to persist for a year in the brains of rats.[117] The brains of rats inoculated with the virus of Rocky Mountain spotted fever were not infectious after a month. Endemic typhus fever can be maintained in native field mice.[118] Gray squirrels, fox squirrels, cottontail rabbits, swamp rabbits, chipmunks and skunks were all found to be susceptible to the virus.[119] Rats were found to harbor typhus rickettsias (murine form) in North China, where it was previously believed that only the epidemic, or human, form existed.[120] All of these studies emphasize the importance of native rodents as a perennial reservoir of typhus fever.

Boston investigators[121] found that by giving typhus-infected rats a diet deficient in riboflavin a greatly increased yield of rickettsias was obtained. A reduction of resistance of animals brought about by a diet deficient in riboflavin might be useful in studying other viruses of low invasiveness for otherwise healthy animals.

Davis and Cox[122] recovered from wood ticks a filter-passing agent similar to the one described by Noguchi in 1926. The agent caused disease when inoculated into guinea pigs, and it could be propagated by transfer from one animal to another. The virus passes through filters which hold back the rickettsias of typhus and spotted fever, and cross immunity tests failed to show any relationship with these infectious agents. The filter-passing agent survived in ticks experimentally infected and in eggs deposited by infected females and was transmitted by the progeny. The agent was not a filtrable virus in the strict sense of the term, since numerous minute rickettsia-like organisms were seen

117. Philip, C. B., and Parker, R. R.: The Persistence of the Viruses of Endemic (Murine) Typhus, Rocky Mountain Spotted Fever and Boutonneuse Fever in Tissues of Experimental Animals, Pub. Health Rep. **53**:1246-1251 (July 22) 1938.

118. Brigham, G. D.: Endemic Typhus Virus in Mice, ibid. **53**:1251-1256 (July 22) 1938.

119. Brigham, G. D.: Susceptibility of Animals to Endemic Virus, Pub. Health Rep. **53**:2078-2079 (Nov. 25) 1938.

120. Wu, C. J., and Zia, S. H.: Isolation of Typhus Fever Virus from House Rats in Peiping, Proc. Soc. Exper. Biol. & Med. **39**:163-165 (Oct.) 1938. Liu, W. T., and Chung, H. L.: A Murine Typhus Virus Isolated from a Patient in Peiping China, ibid. **40**:350-353 (March) 1939.

121. Pinkerton, H., and Bessey, O. A.: The Loss of Resistance to Murine Typhus Infection Resulting from Riboflavin Deficiency in Rats, Science **89**:368-370 (April 21) 1939.

122. Davis, G. E., and Cox, H. R.: A Filter-Passing Infectious Agent Isolated from Ticks: I. Isolation from Dermacentor Andersoni Reactions in Animals, and Filtration Experiments, Pub. Health Rep. **53**:2259-2267 (Dec. 30) 1938. Parker, R. R., and Davis, G. E.: II. Transmission by Dermacentor Andersoni, ibid. **53**: 2267-2270 (Dec. 30) 1938. Cox, H. R.: III. Description of Organism and Cultivation Experiments, ibid. **53**:2270-2276 (Dec. 30) 1938. Dyer, R. E.: IV. Human Infections, ibid. **53**:2277-2282 (Dec. 30) 1938.

in stained sections of tissues from infected animals. The stained organisms look like rickettsias of typhus but also resemble Bartonella bacilliformis of Carrion's disease. They could not be cultivated on special mediums but were cultivated readily in tissue cultures.

One of the investigators of the disease became ill with malaise, pain in the eyes, chilly sensations, sweating, a temperature which reached 40 C. (104 F.) and dropped to normal on the seventh day, and pain and swelling in the joints of the fingers. The leukocytes numbered 8,800 per cubic millimeter. Blood from the patient inoculated into guinea pigs caused the same type of reaction as mentioned in a preceding paragraph. Furthermore, the patient's serum during convalescence protected guinea pigs against infection with the agent under study. Dyer suggests that the disease may be identical with the "Q" fever discovered in Australia, which is also transmitted by ticks. Guinea pigs convalescent from "Q" disease were immune to infection with the rickettsia from Montana.

Of interest is a psittacosis-like atypical pneumonia reported by Rasmussen.[82] He studied 68 cases of an epidemic form of pneumonia which occurs occasionally in the Faroe Islands. He believes that a connection exists between the incidence of the disease and the catching of young marine birds, which may be the source of the infection. Pinkerton [123] reports an instance of anthrax contracted from minks on a fur farm.

An epidemic of paratyphoid fever broke out in a village in Sweden two weeks after an attack of enteritis in a dog.[124] The dog's blood later was found to agglutinate specifically the suspension of the bacillus. Another epidemic of paratyphoid infection in Sweden was also traced to a dog which came from a village in which the disease was prevalent.[125]

Anderson [126] believes that hepatitis in man may be acquired by infection from a similar disease in swine. In swine it is an infectious parenchymal hepatic disease transmissible to rats. No experimental data are offered as to the nature of the infectious agent. Dienes [127] reported an outbreak of hepatitis in Germany.

Ten Broeck and Nelson [128] discovered a highly fatal disease among guinea pigs in their colony of animals. The causative agent seemed

123. Pinkerton, H.: An Outbreak of Anthrax Infection in Minks with Infection of a Ranch Owner, J. A. M. A. **112**:1148-1149 (March 25) 1939.

124. Caspersen, J.: Ein Hund als wahrscheinliche Infektionsquelle eines kleinen Paratyphus-B-Ausbruches, Ztschr. f. Hyg. u. Infektionskr. **120**:611-614 (July) 1938.

125. Magnussen, K. E.: Ein Hund als Ansteckungsquelle von Paratyphusinfektion, Ztschr. f. Hyg. u. Infektionskr. **121**:136-138 (Oct.) 1938.

126. Anderson, T. T.: Investigations on the Etiology of Epidemic Hepatitis, Ugesk. f. læger **100**:777-806 (July 14) 1938.

127. Dienes, H.: Hepatitis epidemica in Dossenheim bei Heidelberg, Ztschr. f. Hyg. u. Infektionskr. **120**:526-538 (June) 1938.

128. Ten Broeck, C., and Nelson, J. B.: A Highly Fatal Disease of Guinea Pigs, Proc. Soc. Exper. Biol. & Med. **39**:572-573 (Dec.) 1938.

to be a filtrable virus. A few young animals became ill, and organ suspensions were injected into other animals. Fever developed after two to five days, leukopenia occurred and the animals given the injections all died in about two weeks. Pneumonia occurred only in animals inoculated intranasally and in those infected by contact. No other lesions were described except enlarged lymph nodes.

Hammon and Enders [129] isolated a virus from cats during a spontaneous epidemic. The virus caused leukocytosis and intestinal lesions, in which inclusion bodies were present.

A curious form of chronic ulcerative cecitis was observed in rats, characterized by chronic lymphangitis, lymphedema and lymphoid hyperplasia of the lymph nodes of the mesentery.[130]

Sabin [131] subjected tissue infected with Toxoplasma to a temperature of — 80 C., killing the organisms, and found unexpectedly a filtrable transmissible agent with neurolytic properties for mice to be present. This agent passed through a 720 but not through a 628 millimicron graded collodion membrane. After it had been inoculated intraocularly in mice, films of the inner contents of the eyes, stained by Giemsa's method, revealed peculiar minute structures. Later experiments suggested that this neurolytic agent was similar to that associated with pleuropneumonia and similar to the one isolated by Findlay and Klieneberger from mice during passage of the viruses of yellow fever and lymphocytic choriomeningitis.[132]

A progressive proliferative polyarthritis with clinical and pathologic similarities to human rheumatoid arthritis was produced experimentally in mice with a filtrable pleuropneumonia-like micro-organism recently isolated from a normal mouse. Sabin [133] suggests investigation to determine whether or not a similar agent may play a role in human rheumatoid arthritis.

Andrei and Ravenna [134] report the development of thromboendocarditis in rabbits after intraperitoneal injection of various substances

129. Hammon, W. D., and Enders, J. F.: A Virus Disease of Cats, Principally Characterized by Aleukocytosis, Enteric Lesions and the Presence of Intranuclear Inclusion Bodies, J. Exper. Med. **69**:327-351 (March) 1937.

130. Jones, B. F., and Stewart, H. L.: Chronic Ulcerative Cecitis in the Rat, Pub. Health Rep. **54**:172-175 (Feb. 3) 1939.

131. Sabin, A. B.: Isolation of a Filtrable, Transmissible Agent with "Neurolytic" Properties from Toxoplasma-Infected Tissue, Science **88**:189-191 (Aug. 26) 1938.

132. Sabin, A. B.: Identification of the Filtrable, Transmissible Neurolytic Agent Isolated from Toxoplasma-Infected Tissue as a New Pleuropneumonia-Like Microbe, Science **88**:575-576 (Dec. 16) 1938.

133. Sabin, A.: Experimental Proliferative Arthritis in Mice Produced by Filtrable Pleuropneumonia-Like Microorganisms, Science **89**:228-229 (March 10) 1939.

134. Andrei, G., and Ravenna, P.: Thromboendocarditis in Rabbits: New Disease Due to Infravirus (?), Arch. Int. Med. **62**:377-383 (Sept.) 1938.

such as human blood, horse serum and milk. The disease, when established, could apparently be transmitted to other rabbits. The observers believe the causative agent to be a filtrable virus, since cultures made from the lesions were sterile. These observations may be of importance with respect to subacute bacterial endocarditis in human beings.

Pasteurella Infections.—Ewing and Fox [135] report the presence in Iowa, Minnesota, Illinois and Ohio of Xenopsylla cheopis, the oriental rat flea capable of transmitting plague. A small epidemic of pneumonic plague broke out in Ecuador in January 1939.

Jellison [136] calls attention to the importance of flesh-eating birds as disseminators of plague. Predatory birds often carry flea-bearing carcasses of small animals great distances and may serve as accidental hosts to fleas of rodents which transmit plague. Casts of birds fed with plague-infected animal tissue were consistently infectious.

Topping, Watts and Lillie [137] report the first case to be recorded in English or American literature of human infection with Pasteurella pseudotuberculosis rodentium, a bacterium associated with disease in animals, particularly rodents. The germ belongs to the Pasteurella group and is closely related to Pasteurella pestis of plague and to Pasteurella tularensis, as I pointed out in 1931. Unfortunately, the confusing term "pseudotuberculosis" was given to the disease. It has no relation to tuberculosis or to Besnier-Boeck disease or to many other conditions which have been called pseudotuberculosis only because of the presence of minute granulomatous lesions. Plette [138] in Holland described a case of pasteurellosis but failed to classify it further.

BACILLARY DISEASES

Undulant Fever.—The cause of the serious epidemic of undulant fever which broke out among students in East Lansing, Mich.,[139] was traced to defective plumbing and a faulty sterilizer in the bacteriologic laboratory. Back-siphonage of incompletely sterilized waste caused the distribution of contaminated water in the building. The situation is reminiscent of the outbreak of amebic dysentery in Chicago as a result of similar defects of plumbing.

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135. Ewing, H. E., and Fox, I.: Occurrence of the Oriental Rat Flea in the Interior of the United States, Science **88**:427 (Nov. 4) 1938.

136. Jellison, W. L.: Sylvatic Plague: Studies of Predatory and Scavenger Birds in Relation to Its Epidemiology, Pub. Health Rep. **54**:792-798 (May 12) 1939.

137. Topping, N. H.; Watts, C. E., and Lillie, R. D.: A Case of Human Infection with B. Pseudotuberculosis Rodentium, Pub. Health Rep. **53**:1340-1352 (Aug. 5) 1938.

138. Plette, J. G.: Pasteurellose bij den mensch, Nederl. tijdschr. v. geneesk. **82**:6106-6110 (Dec. 24) 1938.

139. Medical News, J. A. M. A. **112**:653 (Feb. 18) 1939.

According to Evans, Robinson and Baumgartner,[140] at the National Institute of Health, no single test other than the isolation of Brucella from the patient can be relied on with certainty for diagnosis. The blood of 4 of 7 patients from which Brucella was isolated gave a negative agglutination reaction. A negative agglutination reaction cannot be regarded as evidence against infection, but a positive reaction indicates the presence of latent or active infection. A positive skin test is less reliable than a positive agglutination test, and the opsonocytophagic test is least reliable of all. All three tests gave negative results in 3 proved cases of brucelliasis. Calder, Steen and Baker[141] point out the constancy of the normal or low leukocyte count and of active lymphocytosis in brucelliasis. In my experience, the low leukocyte count and relative or absolute lymphocytosis were the most constant of various laboratory observations among 30 patients with the disease.

Tuberculosis.—The controversy concerning the value or the harm of hypersensitivity in tuberculosis is still unsettled. Different investigators, using different methods, come to opposite conclusions. For example, Willis and his group[142] find that desensitized guinea pigs have extensive infections. Animals never permitted to become allergic die from tuberculosis before the control animals. According to Freund and Opie,[143] animals sensitized and immunized are more resistant to infection, but there is no correlation between the intensity of sensitization or the titer of antibodies and resistance to infection. Follis,[144] on the other hand, shows that animals infected with tubercle bacilli and prevented from becoming hypersensitive show less caseation than animals that become hypersensitive. Corper and Cohn[145] point out the striking difference between the specific immune and the accompany-

140. Evans, A. C.; Robinson, F. H., and Baumgartner, L.: Studies on Chronic Brucellosis: IV. An Evaluation of the Diagnostic Laboratory Tests, Pub. Health Rep. **53**:1507-1525 (Aug. 26) 1938.

141. Calder, R. M.; Steen, C., and Baker, L.: Blood Studies in Brucellosis, J. A. M. A. **112**:1893-1898 (May 13) 1939. Munger, M., and Huddleson, T. F.: A Preliminary Report of the Blood Picture in Brucellosis, J. Lab. & Clin. Med. **24**:617-619 (March) 1939. Schmid, N.: Blood and Bone Marrow in Bang's Disease (Brucella Abortus Infection), Schweiz. med. Wchnschr. **69**:191-192 (March 4) 1939.

142. Willis, H. S.; Woodruff, C. E.; Kelly, R. G., and Voldrick, M.: Allergic and Desensitized Guinea Pigs, Am. Rev. Tuberc. **38**:10-26 (July) 1938.

143. Freund, J., and Opie, E. L.: Sensitization and Antibody Formation with Increased Resistance to Tuberculous Infection Induced by Heat Killed Tubercle Bacilli, J. Exper. Med. **68**:273-298 (Aug.) 1938.

144. Follis, R. H.: The Effect of Preventing the Development of Hypersensitivity in Experimental Tuberculosis, Bull. Johns Hopkins Hosp. **63**:283-304 (Nov.) 1938.

145. Corper, H. J., and Cohn, M. L.: The Effects of Tuberculoprotein, J. A. M. A. **112**:403-408 (Feb. 4) 1939.

ing allergic features of tuberculosis, the former giving protection and the latter giving a peculiar form of intoxication.

Feldman and Baggenstoss [146] examined encapsulated, caseous or calcified areas in the pulmonary tissues or tracheobronchial lymph nodes from 68 patients who died from causes other than tuberculosis. Tubercle bacilli were found in only a single instance. The authors believe that the "primary complex" in most cases of healed tuberculosis in adults seldom contains viable tubercle bacilli and that endogenous infection is unlikely to occur from old capsulated or calcified areas.

Seibert, Pedersen and Tiselius [147] applied the Svedberg ultracentrifuge in studies on the chemical and physical nature of tuberculin.

McKinney and Mellon [148] report derivation of the mucoid (M) phase of Mycobacterium tuberculosis (H-37) in cultures in alkaline neopeptone glycerol broth.

Myers [149] defends his methods of detecting tuberculosis against the unfavorable views of Lumsden. The tuberculin test, when performed properly, is of great assistance in recognizing this disease. Unfortunately, like other tests applied to the skin, it is occasionally unreliable, but the number of cases in which it fails to indicate tuberculosis is insignificant as compared with the number in which it is positive. Roentgenograms, he points out, are highly unreliable in making an etiologic diagnosis. It is impossible to differentiate shadows cast by bone, calcium and dense fibrous tissue, respectively, and other conditions besides tuberculosis may cause calcification in the lungs; about 12 per cent of tuberculous areas may be obscured by the heart, diaphragm and other opaque parts; early tuberculous lesions may be microscopic in size, and a number of other possibilities make up an 80 per cent handicap for roentgenographic examination as a method of diagnosis.

Myer's views concerning the shortcomings of roentgenographic diagnosis could, I believe, be extended to other fields. As I stated at the May 1938 meeting of the American Medical Association, roentgenologists often exceed their limitations when they report as an "abscess" an area of rarefaction about the root of a tooth or as

146. Feldman, W. H., and Baggenstoss, A. H.: The Residual Infectivity of the Primary Complex of Tuberculosis, Am. J. Path. **14**:473-490 (July) 1938.

147. Seibert, F. B.; Pedersen, K. O., and Tiselius, A.: Molecular Weight, Electrochemical and Biological Properties of Tuberculin Protein and Polysaccharide Molecules, Am. Rev. Tuberc. **38**:399-409 (Oct.) 1938.

148. McKinney, R. A., and Mellon, R. R.: Variability of Tubercle Bacilli: I. Mucoid Phase of the Human Type Strain H-37, Proc. Soc. Exper. Biol. & Med. **40**:298-301 (Feb.) 1939.

149. Myers, J. A.: The Detection of Tuberculosis, J. A. M. A. **112**:1904-1910 (May 13) 1939.

"sinusitis" a cloudiness of one or more of the nasal accessory sinuses. It is impossible on the basis of rarefaction or shadows without clinical symptoms or signs to determine the presence or absence of infection with certainty, and many unnecessary operations, I believe, have been performed on such weak evidence. A diagnosis should be arrived at only after complete study with all the means available, of which roentgenography is only one, but a valuable one when properly used.

Bacillary Dysentery.—Brown and Bargen [150] studied 140 patients who had had bacillary dysentery in an epidemic sixteen years ago to find whether ulcerative colitis was a common sequel. Of the patients who could be traced, 77 had not had any symptoms of bowel trouble since their attack, and only 1 had chronic ulcerative colitis, although 45 still had Shiga dysentery bacilli in the stool. The evidence does not favor the view that acute bacillary dysentery is a common precursor of chronic ulcerative colitis.

Schiff [151] describes a few cases of infection among children in which a "new" type of so-called paratyphoid bacilli, namely, "Salmonella Panama," was isolated. The "paratyphoid bacilli" commonly cause food poisoning. The three main types of this group of bacilli are: Bacterium, or Salmonella, aertryke, Bacterium, or Salmonella, enteritidis and Bacterium, or Salmonella, suipestifer. It appears that, as in the case of pneumococcus, many other types may exist, of which the type Panama may be one. The bacillus was first isolated by Jordan from soldiers suffering from food poisoning in Panama and was identified by Kauffmann in Copenhagen.

Felsen and Osofsky [152] suggest that acidity of the stomach is an effective barrier against infections with dysentery bacilli. Filtered gastric juice of p_H 5.5 or less is bactericidal for Duval-Sonne dysentery bacilli.

Note is made [152a] of the relative absence of acute amebic dysentery in persons unusually exposed to infection. It is probable that some degree of immunity may be acquired as a result of repeated exposure to amebic infection or that various strains of Endamoeba histolytica differ in their invasiveness.

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150. Brown, P. W., and Bargen, J. A.: Bacillary Dysentery: Late Results and Relationship to Chronic Ulcerative Colitis, Am. J. Digest. Dis. **5**:562-565 (Nov.) 1938.

151. Schiff, F.: Salmonella Panama: Occurrence in Serious Infections of Infants in New York City, J. A. M. A. **111**:2458-2460 (Dec. 31) 1938.

152. Felsen, J., and Osofsky, A. G.: Gastric Barrier in Bacillary Dysentery, Arch. Int. Med. **63**:64-70 (Jan.) 1939.

152a. Spector, B. K.; Hardy, A. V., and Mack, M. G.: Studies of the Acute Diarrheal Diseases, Pub. Health Rep. **54**:1105-1113 (June 23) 1939.

Tetanus.—Extensive research on tetanus by Abel and his associates[153] during the past few years led to the impression that the incidents which occurred during the first few hours after infection determined whether the disease would end in death or recovery. From animal experiments it seemed that no amount of antitoxin injected after the toxin once became fixed to nerve tissue would be of any avail in preventing death. Because of subsequent experiments made before Abel's death, this view had to be modified. Although large amounts of antitoxin will not save an animal given a lethal injection of toxin if the delay is too long or if symptoms of descending tetanus have begun, it is still obligatory for physicians to use antitetanic serum in accordance with present usage. In dealing with tetanus in man as compared with experimentally infected animals none of the factors are under control, and there is no way of learning whether a lethal dose of toxin has been fixed or not. It is not known how rapidly or how long toxin is formed at the site of infection. Contrary to general belief,[153a] the timely injection of a large amount of antitetanic serum neutralizes fixed toxin and prevents it from exerting its usual fatal action. In animals, after injection of from 3 to 10 lethal doses of toxin the period in which neutralization of toxin and saving of life may be accomplished lasts from forty to twenty-four hours, depending on the amount of toxin injected. In all cases, however, antitoxin given after the period of incubation has merged into the period of onset of symptoms fails to save life. Antitetanic serum is therefore not entirely devoid of curative properties, provided it is given in large amounts as soon as possible after infection.

Another interesting feature is that biologic assays made of spinal cords after they have "fixed" the toxin give no indication of its presence, suggesting that it has been chemically bound, changed or denatured.[153b] Abel[153c] defends his theory against Doerr's criticism and shows beyond doubt that tetanus toxin is carried to the central neurons by way of the blood stream and not by way of the axis-cylinders of motor nerves.

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153. (*a*) Abel, J. J.; Hampil, B.; Jonas, A. F., Jr., and Chalian, W.: Researches in Tetanus: VII. (1) The Time Required for the Fixation of a Fatal Quantity of Tetanus Toxin; (2) The Return Passage of Toxin by Way of the Lymphatic Capillaries to the Cardiovascular System; (3) The Return Passage as the Basis of a Method for the Approximate Determination of the Volume of Lymph in the Closed Lymphatic System, Bull. Johns Hopkins Hosp. **62**:522-563 (May) 1938. (*b*) Abel, J. J.; Firor, W. M., and Chalian, W.: Researches on Tetanus: VIII. At What Point in the Course of Tetanus Does Antitetanic Serum Fail to Save Life? ibid. **62**:610-633 (June) 1938; (*c*) IX. Further Evidence to Show that Tetanus Toxin Is Not Carried to Central Neurons by Way of the Axis Cylinders of Motor Nerves, ibid. **63**:373-403 (Dec.) 1938.

Hertz [154] reports 3 cases of failure of tetanus antitoxin used prophylactically to save life. In another case tetanus bacilli were found in a scar ten years after an attack of the disease.[155]

COCCAL DISEASES

Subacute Bacterial Endocarditis.—Poston and Orgain [156] were unable to demonstrate any significant specific serologic evidence of immunity in patients during the active bacteremic stage of any type of endocarditis, including that caused by Streptococcus viridans. Immune bodies developed coincidentally with the disappearance of bacteremia. Their work has raised the perennial question as to the actual relation of streptococci to the disease. Despite the frequent association of Str. viridans with the disease, numerous observers, including myself, have suspected that some other agent may be the underlying cause, the streptococcus being a secondary invader. Str. viridans has not yet been conclusively shown to be a primary cause of any disease. Its mere presence in a diseased area does not prove its pathogenicity.

According to Moran,[157] the physiologic and fermentative reactions of streptococci from 20 patients with endocarditis permit their classification as members of the group of "salivary" streptococci or enterococci. This suggests that the streptococci concerned came from an endogenous source—somewhere in the respiratory tract or gastrointestinal tract.

Staphylococcus Osteomyelitis.—Thompson and Dubos [158] succeeded in causing osteomyelitis in rabbits by injecting a culture of a Staphylococcus intravenously. When large amounts of culture were injected, infection was apt to be fulminating and to end in early death. The injection of small amounts in normal rabbits or of large amounts in rabbits previously immunized was followed by a more chronic type of infection. Of 31 rabbits studied, a prolonged illness of one to three weeks was established in 22, and in 18 of these osteomyelitis developed. There was a predilection of the bacteria for the metaphyses of the long

154. Hertz, J.: Failure of Tetanus Prophylaxis, Ugesk. f. læger **100**:871-877 (Aug. 4) 1938.

155. Bonney, V.; Box, C., and MacLennan, J.: Tetanus Bacilli Recovered from the Scar Ten Years After an Attack of Postoperative Tetanus, Brit. M. J. **2**:10-11 (July 2) 1938.

156. Poston, M., and Orgain, E. S.: Immunologic Studies on Patients Suffering from Bacterial Endocarditis, Proc. Soc. Exper. Biol. & Med. **40**:284-286 (Feb.) 1939.

157. Moran, H.: Classification of Streptococci from Cases of Endocarditis, Proc. Soc. Exper. Biol. & Med. **38**:805-808 (June) 1938.

158. Thompson, R. H. S., and Dubos, R. J.: Production of Experimental Osteomyelitis in Rabbits by Intravenous Injection of Staphylococcus Aureus, J. Exper. Med. **68**:191-206 (Aug.) 1938.

bones, similar to that which is commonly observed in children. Multiple abscesses of the kidneys were present in most of the animals.

Meningitis.—Cowan,[159] studied bacteria isolated from cerebral infections in 5 patients on whom operations were performed. Atypical gram-positive or gram-negative bacilli and a gram-negative capsulated coccus were recovered. These bacteria would ordinarily be regarded as saprophytes or contaminants, but he believes that they actually caused infection of the brain because of their placement in sites ordinarily never exposed to bacteria. The coccus which was isolated was thought to be the same as Diplococcus mucosus of von Lingelsheim. It has certain resemblances to atypical gram-negative cocci which Koucky and I obtained from a patient with meningitis.[160]

OTHER DISEASES

Infectious Diseases of the Gastrointestinal Tract of Unknown Origin.—Boardman[161] reports a fairly widespread outbreak of acute gastroenteritis in San Francisco. The disease was characterized by an acute and sudden onset of nausea, abdominal cramps, watery diarrhea, sometimes vomiting, slight headache, general aching, dizziness and fever occasionally as high as 40 C. (104 F.). In some cases there was evidence of an infection of the upper portions of the respiratory tract a day or two before the onset of general symptoms. The leukocyte counts varied from 10,100 to 20,000. Bacilli of the typhoid-dysentery group were isolated from 10 of 28 patients, but Boardman does not feel convinced of their etiologic significance. He calls attention to the frequency of similar outbreaks of gastrointestinal disease in sporadic or epidemic form elsewhere and suggests that defective plumbing may be responsible for its spread. He suggests that the infection may be caused by a filtrable virus, which may also be carried in the secretions of the nose and throat. A similar disease was described by Spencer in 1930 and by Willman in 1933, and one occurred in Chautauqua County, N. Y., in March 1939.

A supposedly "new" disease, called epidemic nausea and vomiting, has been noted in Europe since 1935.[162] It may be the same as that recorded by Boardman and others. The illness is mild, seldom lasts longer than forty-eight hours and is characterized by nausea, vomiting,

159. Cowan, S. T.: Unusual Infections Following Cerebral Operations, Lancet **2**:1052-1054 (Nov. 5) 1938.

160. Reimann, H. A., and Koucky, R. W.: Meningitis Caused by Atypical Gram-Negative Cocci, J. Bact. **37**:401-410 (April) 1939.

161. Boardman, W. W.: Acute Infectious Gastro-Enteritis, Am. J. M. Sc. **196**:833-840 (Dec.) 1938.

162. Gray, J. D.: Epidemic Nausea and Vomiting, Brit. M. J. **1**:209-211 (Feb. 4) 1939.

giddiness, slight fever and diarrhea. Such epidemic illnesses are perhaps very common but because of their mildness and brief duration are seldom studied carefully or are mistaken for bacillary dysentery or food poisoning.

A mild epidemic disease called vesicular pharyngitis and stomatitis affected 106 persons in a boys' camp.[163] Vesicles of the faucial pillars, soft palate and tonsillar tissue and fever were the chief signs, and headache, malaise and sore throat were the chief symptoms. On clinical evidence alone it was suggested that the disease was of herpetic origin.

Ulcerative Colitis.—Three papers[164] on ulcerative colitis leave one with a rather pessimistic attitude as far as knowledge of the cause of the disease or successful management or prevention of it is concerned. Mackie[164a] did not observe much, if any, benefit after the use of vaccines, antiserums, bacteriophage or surgical procedures. Jones[164b] is not enthusiastic about surgical treatment except when only the left half of the colon is diseased. Willard and his associates[164c] find that no single therapeutic measure produces striking results and that often the entire armamentarium fails to influence the course. In their experience surgical intervention was accompanied by a death rate of 73 per cent.

In a discussion of these three papers Bloomfield points out an interesting analogy of ulcerative colitis with several other diseases of a semiinflammatory-semidegenerative nature, namely, iritis, choroiditis, arthritis and hepatitis, in the study of which little or no progress in knowledge has been made. Aaron, discussing the striking effects claimed to occur after liver preparations have been given to patients, stated that this treatment merely corrects the dietary deficiency which may follow injudicious restriction of food.

Acute Rheumatic Fever.—Many papers on rheumatism and arthritis were discussed by Hench and his associates[165] in their fifth annual review of rheumatism and need not be referred to again here.

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163. Levine, H. D.; Hoerr, S. O., and Allanson, J. C.: Vesicular Pharyngitis and Stomatitis: An Unusual Epidemic of Possible Herpetic Origin, J. A. M. A. **112**:2020-2022 (May 20) 1939.

164. (*a*) Mackie, T. T.: The Medical Management of Chronic Ulcerative Colitis, J. A. M. A. **111**:2071-2076 (Dec. 3) 1938. (*b*) Jones, T. E.: The Surgical Treatment of Ulcerative Colitis, ibid. **111**:2076-2078 (Dec. 3) 1938. (*c*) Willard, J. H.; Pessel, J. F.; Hundley, J. W., and Bockus, H. L.: The Prognosis of Ulcerative Colitis, ibid. **111**:2078-2084 (Dec. 3) 1938.

165. Hench, P. S.; Bauer, W.; Dawson, M. H.; Hall, F.; Holbrook, W. P., and Key, J. A.: The Problem of Rheumatism and Arthritis: Review of American and English Literature for 1937, Ann. Int. Med. **12**:1005-1104 (Jan.); 1295-1374 (Feb.) 1939.

Eagles and his associates [166] were unable to show that the virus-like bodies suspected of causing rheumatic fever were pathogenic for animals. Keil [167] made a critical review of papers pertaining to the subcutaneous nodule of rheumatism. He believes, as I do, that although the lesions in acute rheumatic fever may resemble histologically those found in rheumatoid arthritis, they need not be considered identical. It seems unsafe to establish the etiologic identity of two diseases on the basis of histologic changes when the clinical differences are usually so distinctive.

Salvesen [168] found nephritis to follow acute rheumatic fever in 4.7 per cent of 212 cases. He describes in detail 6 cases in which nephritis supposedly was the result of rheumatic fever.

Rheumatic pericarditis was found to be far less serious than rheumatic valvulitis.[169]

Swift and Brown [170] introduced exudates from patients with rheumatic fever onto chorioallantoic membranes, intranasally into mice and intraocularly into rabbits. Characteristic lesions developed in mice as pneumonia and in rabbits as iritis. From these lesions a filtrable organism was obtained which produced a pleuropneumonia-like illness in animals. Similar material obtained from nonrheumatic patients failed to cause lesions or to show any unusual organisms. The etiologic significance of this discovery in respect to the cause of rheumatic fever is under study.

Malaria.—Investigators in the Southern States are finding an acridine derivative (atabrine) of value in the control of malaria.[171] Cures in 90 per cent of the patients are claimed. One study showed the

166. Eagles, G. H.; Evans, P. R.; Fisher, A. G. T., and Keith, J. D.: Infection Experiments with Virus-like Bodies from Rheumatism, J. Path. & Bact. **46**:481-495 (May) 1938.

167. Keil, H.: Rheumatic Subcutaneous Nodules and Simulating Lesions, Medicine **17**:261-380 (Sept.) 1938.

168. Salvesen, H. A.: Rheumatic Fever and Nephritis, Acta med. Scandinav. **96**:304-314 (Sept. 3) 1938.

169. Massie, E., and Levine, S. A.: The Prognosis and Subsequent Developments in Acute Rheumatic Pericarditis, J. A. M. A. **112**:1219-1223 (April 1) 1939.

170. Swift, H. F., and Brown, T. M.: Pathogenic Pleuropneumonia-like Microorganisms from Acute Rheumatic Exudates and Tissues, Science **89**:271-272 (March 24) 1939.

171. Hill, R. A., and Goodwin, M. H.: Two Years' Observation on the Use of Atabrine as Prophylactic Agent in Malaria, Am. J. Trop. Med. **18**:339-346 (July) 1938. Holton, C. F., and Winchester, M. E.: Use of Atabrine in the Treatment and Control of Malaria Among a Group of Industrial and Agricultural Employees in Georgia, J. M. A. Georgia **27**:299-303 (Aug.) 1938. Gill, D. G., and Smith, M.: Atabrine as Malarial Prophylactic Agent: Experiment with Drug in a Region in Central Alabama, J. M. A. Alabama **8**:66-67 (Aug.) 1938.

blood parasite index reduced from 16.9 to 0.3 per cent after two years of prophylaxis with this drug. Proske and Watson [172] have devised a test for malaria based on a protein tyrosine reaction of the serum. The test is based on the chromogenic property of the protein, which can be measured against the color given by tyrosine in the presence of a phenol reagent. The tyrosine index for euglobulin in normal blood serum rests between 50 and 80 while that of serum from patients with malaria is increased from 80 to 280 or more. The test is not strictly specific for malaria, but a positive reaction is present in so many cases of this infection as to make it a valuable diagnostic aid.

Kitchen, Webb and Kupper [173] studied the effect of malaria on the development of the Wassermann reaction in nonsyphilitic patients. Positive reactions were obtained in every case. The reaction developed usually in the third and fourth week after infection and lasted more than three to four weeks in nearly half the patients studied.

When Plasmodium vivax and Plasmodium malariae were inoculated together for the treatment of dementia paralytica in 16 patients, both types of parasites were found in the blood, but soon one or the other become dominant.[174] P. vivax was usually more successful in surviving. The authors suggest that in many more cases of naturally acquired disease than is believed the infection is of the mixed type.

Yellow Fever.—Two varieties of mosquitoes besides Aedes aegypti may transmit jungle yellow fever.[175] New Jersey mosquitoes were also found to be capable of transmitting the disease to monkeys.[176] Because of rapid transportation by air from South America, the director of health in Miami, Fla., has ordered all persons who have been in areas that are actually or potentially centers of yellow fever to report within twenty-four hours after arrival and be kept under surveillance for six days.[177] In one study, however, no live mosquitoes

172. Proske, H. O., and Watson, R. B.: The Protein Tyrosin Reaction: A Biochemical Diagnostic Test for Malaria, Pub. Health Rep. **54**:158-172 (Feb. 3) 1939.

173. Kitchen, S. F.; Webb, E. L., and Kupper, W. H.: The Influence of Malarial Infections on the Wassermann and Kahn Reactions, J. A. M. A. **112**: 1443-1449 (April 15) 1939.

174. Mayne, B., and Young, M. D.: Antagonism Between Species of Malaria Parasites in Induced Mixed Infections, Pub. Health Rep. **53**:1289-1291 (July 29) 1938.

175. Shannon, R. C.; Whitman, L., and Franca, M.: Yellow Fever Virus in Jungle Mosquitoes, Science **88**:110-111 (July 29) 1938.

176. Bennett, B. L.; Baker, F. C., and Sellards, A. W.: The Behavior of the Virus of Yellow Fever in the Mosquito, Aedes Triseriatus, Science **88**:410-411 (Oct. 28) 1938.

177. Miami Health Officer Acts to Prevent the Introduction of Yellow Fever. Pub. Health Rep. **53**:1621 (Sept. 9) 1938.

of the species Aedes aegypti were found on incoming aircraft in 1938, but several other varieties, both alive and dead, were.[178]

The Rockefeller Foundation,[179] in cooperation with the Brazilian government, has vaccinated over 1,000,000 persons against yellow fever. Among those vaccinated, 8 contracted yellow fever, 6 of them within four days of vaccination. Local physicians reported a sudden reduction in number of cases shortly after the mass vaccination.

Emmons[180] observed a species of Actinomyces in 37 per cent of 200 pairs of tonsils removed from patients for other reasons. It seems probable that these fungi are commonly present in normal mouths and throats.

McMaster and Gilfillan[181] report 24 cases of osteomyelitis caused by Coccidioides.

Pons and Julianelle[182] isolated Listerella monocytogenes from the blood of a patient with infectious mononucleosis. The bacterium when injected into rabbits caused characteristic lymphocytic-monocytic changes. Schultz, Terry and Brice[183] suggest that Listerella monocytogenes may be a cause of meningoencephalitis in man. It must be decided, of course, whether this bacterium was the cause of the conditions in patients from whom it was recovered or whether it was merely a saprophyte.

MISCELLANEOUS STUDIES

Dresel[184] apparently caused transformation in the test tube of nonpathogenic Bacterium typhi flavum into virulent typhoid bacilli. The interpretation of his work as type transformation has support in observations reported in 1938 in which similar changes from chromogenic bacteria to nonchromogenic ones were reported.[185] In a similar vein,

178. Welch, E. V.: Insects Found on Aircraft at Miami, Fla., in 1938, Pub. Health Rep. **54**:561-566 (April 7) 1939.

179. Fosdick, R. B.: The Rockefeller Foundation: A Review for 1938, New York, The Rockefeller Foundation, 1939, p. 12.

180. Emmons, C. W.: The Isolation of Actinomyces Bovis from Tonsillar Granules, Pub. Health Rep. **53**:1967-1975 (Nov. 4) 1938.

181. McMaster, P. E., and Gilfillan, C.: Coccidioidal Osteomyelitis, J. A. M. A. **112**:1233-1237 (April 1) 1937.

182. Pons, C. A., and Julianelle, L. A.: Isolation of Listerella Monocytogenes from Infectious Mononucleosis, Proc. Soc. Exper. Biol. & Med. **40**:360-361 (March) 1939.

183. Schultz, E. W.; Terry, M. C.; Brice, A. T., Jr., and Gebhardt, L. P.: Listerella Monocytogenes: A Cause of Meningoencephalitis in Man, Proc. Soc. Exper. Biol. & Med. **38**:605-608 (June) 1938.

184. Dresel, E. G., and Graf, W.: Neue Ergebnisse über das Bact. typhi flavum, Arch. f. Hyg. **119**:153-167, 1937.

185. Reimann, H. A.: The Significance of Bacterial Type Transformation in Infectious Disease and Epidemiology, Tr. A. Am. Physicians **53**:270-273, 1938.

Horgan [186] reports the transformation of variola to vaccinia virus by passage of the former intratesticularly in rabbits. Findlay and MacCallum [187] report further studies on the transformation of a neurotropic strain of yellow fever virus into a pantropic one. Each of these observations suggests that type transformation may be a natural phenomenon among bacteria and viruses.

Cold Vaccines.—The study of Diehl and his associates [188] on the use of vaccines in the prevention or the treatment of colds is of great value in combating many claims by commercial concerns which sell the so-called "cold vaccines." In carefully controlled work it was shown that vaccines taken orally were of no value whatever; vaccines injected subcutaneously seemed to reduce the incidence of colds about 25 per cent, which is not sufficiently great to justify the time and expense of vaccination. There was no evidence that vaccines reduce the incidence of complications of colds. The results of others [189] are in agreement.

Similar conclusions were made by Bock,[190] who studied 1,667 cases of acute infection of the respiratory tract. In his cases fatigue of body and mind was an important factor in precipitating such infections. He advises against the use of energetic local treatment, which may aggravate and prolong the illness.

Jefferson Hospital.

186. Horgan, E. S.: The Experimental Transformation of Variola to Vaccinia, J. Hyg. **38**:702-715, 1938.

187. Findlay, G. M., and MacCallum, F. O.: Spontaneous Variation in the Neurotropic Strain of Yellow Fever Virus, Brit. J. Exper. Path. **19**:367-442 (Dec.) 1938.

188. Diehl, H. S.; Baker, A. B., and Cowan, D. W.: Cold Vaccines: An Evaluation Based on a Controlled Study, J. A. M. A. **111**:1168-1173 (Sept. 24) 1938.

189. Hauser, I. J., and Hauser, M. J.: Controlled Study of "Cold Vaccines," Arch. Otolaryng. **29**:704-719 (April) 1939.

190. Bock, A. V.: Clinical Observations, Complications and Treatment of Acute Upper Respiratory Tract Infections, Ann. Int. Med. **12**:317-322 (Sept.) 1938.

Book Reviews

Rheumatische Kreislaufschädigungen. By Dr. Siegfried Dietrich. Price, 6.75 marks, unbound. Pp. 204. Dresden: Theodor Steinkopff, 1938.

This volume is the seventh of a series dealing with the problem of rheumatism recently published in Germany under the editorship of Prof. Rudolph Jürgens. The appearance of the series, according to the editor, is a response to recent recognition among both political and medical circles in the German Reich of the enormous sociologic problem arising from rheumatic diseases. Each volume is intended to present to the practitioner a single facet of this problem in a unified manner.

The book is a reasonably thorough review of well grounded and generally accepted data with regard to the rheumatic state, and the author has included a presentation of much important recent literature dealing with studies of etiologic factors, histopathologic picture, natural history of the disease, modern diagnostic methods and recent views on drug therapy. A carefully compiled bibliography increases the value of the book as a reference tool.

The author has forcefully indicated how preoccupation with isolated features of rheumatic fever, such as chorea, acute arthritis or physical signs of chronic valvular disease, may detract from appreciation of the nature of the diffuse process which constitutes the rheumatic state. The great importance of the myocardial lesion is well stressed. The early clinical phenomena of rheumatic fever are carefully described in an effort to encourage earlier recognition and more adequate early treatment. Lengthy discussions of the end product of rheumatic fever, the failing heart resulting from mechanical impediments of deformed valves, are avoided.

Although the subject matter is generally treated objectively, the author appears to be personally committed on several points in which he is probably in error. Thus, Dietrich has accepted the existence of a chronic inflammatory disease of the heart arising from focal infection, citing the literature which is said to establish the pathologic and clinical features of this disease; tuberculous rheumatoid arthritis is considered by him to be an established entity which must be included in differential diagnosis of rheumatic fever; he believes that chronic progressive deforming arthritis may at times be due to rheumatic fever; a specific disease of the coronary arteries due to rheumatic fever and leading to infarction of the heart is likewise discussed in the text. In the sections concerned with prevention the author urges a rigorous life filled with exercise calculated to harden the body, and even active army service or "work-service" is said to be useful for preventing rheumatic fever. The importance of better housing, sanitation, warmth and sufficient food does not appear to be adequately stressed.

The book is, nevertheless, a rather conservative presentation of current knowledge concerning rheumatic fever. It is clear and thorough and as a source of information on this disease is fairly complete.

Malignant Tumors of the Skeletal Muscles, Fasciae, Joint Capsules, Tendon Sheaths and Serous Bursa. Acta radiologica, Supplement 36. By Gunnar Jönsson. Pp. 304, with 20 illustrations. Stockholm: P. A. Norstedt & Son, 1938.

This treatise reviews in a concise and well presented manner the material at Radiumhemmet, the literature and a historical sketch of the present knowledge concerning malignant tumors of muscle and fascial sheaths as well as those of joint capsules, tendon sheaths and serous bursae. The author has clearly demonstrated the inadequacies of a histologic classification of such tumors and has emphasized that in spite of existing hiatuses in the knowledge, a histogenetic classification together with topographic considerations lends itself to greater accuracy in foretelling the behavior of a given tumor, in selecting the most appropriate type of therapy and in establishing an intelligent prognosis. Dr. Jönsson's

historical sketches do much to elucidate the existing chaos of nomenclature. Excellent series of case histories supplemented by numerous photomicrographs illustrate the various types of tumor.

The analysis of the material at Radiumhemmet, though not extensive enough for statistical study, is of interest. This material was divided into two main groups: (*a*) malignant muscular and fascial tumors and (*b*) malignant synovial tumors. The malignant muscular and fascial tumors showed the following histologic types: rhabdomyosarcoma, spindle cell sarcoma, fibrosarcoma, myxoliposarcoma and round cell sarcoma. The malignant synovial tumors were divided into the two groups of synovialoma and synovial fibrosarcoma.

The results obtained from the author's study are significant. In a series of 38 cases of rhabdomyosarcoma the tumor was characterized by a rapid course, early distant metastases and only slight radiosensitivity. Fifteen cases of spindle cell sarcoma showed a slower course, no development distant metastases until relatively late and not infrequently a pronounced radiosensitivity. As a whole, this group was moderately radiosensative. In a series of 10 cases of fibrosarcoma the tumor showed slow growth and low degree of radiosensitivity, and it was not clear whether or not metastases ever occurred. In this series the prognosis for the group was excellent, all the patients being alive and well up to the time of the report, the shortest interval being eighteen months.

Adventures in Respiration: Modes of Asphyxiation and Methods of Resuscitation. By Yandell Henderson. Pp. 316. Baltimore: Williams & Wilkins Company, 1938.

In this interesting book the author traces the historic milestones leading to the present understanding of the physiology of respiration and discusses the value and rationale of using carbon dioxide in the treatment of various asphyxial states. Arrangement of the subject matter in narrative form, as an adventure of the author in research over a period of years, endows facts and theories with charm and personal interest. The first part of the book is devoted to a consideration of shock, the control of breathing and blood alkali and the "fallacy of asphyxial acidosis," in which discussion the conception of "acarbia" as induced by "hyperpnein" is suggested as a substitute for the theory of "acidosis" induced by lactic or other acid. There are several chapters dealing with the physiologic basis of mountain sickness and acclimatization, carbon monoxide asphyxia and asphyxia of the newborn. The therapeutic value and methods of administration of carbon dioxide in these conditions and in anesthesia, atelectasis and pneumonia are described in detail. In a discussion of circulatory failure and asphyxia the author emphasizes the role of muscle tonus in the control of the circulation and postulates that a failure of muscle tonus may be a major cause of failure of the circulation. Some of the theories championed remain controversial, but the facts of normal and disturbed respiration are clearly delineated, and the whole makes stimulating and enjoyable reading. Evidence of the therapeutic efficacy of carbon dioxide is convincingly presented.

Las arritmias en clínica. By Dr. Antonio Battro. Pp. 476, with 201 illustrations. Buenos Aires: El Ateneo, 1937.

Dr. Battro has again scored by presenting an excellent book. In this volume he has thoroughly gone into the subject of the arrhythmias from the diagnostic, prognostic and therapeutic standpoints. The general anatomy of the heart and especially the blood supply is well illustrated. His brief discussion of the physiology and the many graphic tracings are both timely and illustrative of the thoroughness with which the subject is presented.

Basically the book is divided into chapters dealing with the arrhythmias under the following headings: (1) chronotropic arrhythmia, (2) bathmotropic arrhythmia, (3) dromotropic arrhythmia, (4) fibrillation and flutter and (5) inotropic arrhythmia.

The bibliography is thorough, covering fifty pages, and includes a large percentage of references to American authors.

Medical Applications of the Short Wave Current. By William Bierman, M.D. Including a discussion of the physical and technical aspects by Myron M. Schwarzschild, M.A. Price, $5. Pp. 379. Baltimore: William Wood & Company, 1938.

The author presents in this volume the theoretic and practical principles of therapeutic application of the short wave current. The text is divided into two parts. Part I, consisting of five chapters, is devoted to fundamental considerations, and Part II, containing three chapters, to clinical considerations.

Chapter I is devoted to the history of the development of the short wave current and is concise and clear. Chapter II, which deals with the physics of the short wave current, was written by a physicist familiar with the medical requirements of short wave therapy. This is a valuable contribution to the volume from the point of view of the average physician, as many of the mysteries of the mode of action of short wave therapy are cleared up.

The third chapter deals with the determination of temperature in the living human being. The physiologic responses of the various organs and systems to local heat and local short wave currents are discussed in chapter IV. The injurious effects of this form of therapy are covered in this chapter.

The fifth chapter, on the specificity of the short wave current, is of considerable interest. While the author believes that the effects of short wave therapy are due solely to the production of heat, full consideration is given to the other theories, especially to that of specificity.

Chapter VI considers technic and methods of application of short wave therapy. The directions given are clear and complete, and the various applicators employed are well illustrated and carefully described.

The clinical applications of this form of therapy in various clinical conditions are discussed in chapters VII and VIII. The clinical results to be expected in each condition are also noted. Due emphasis is devoted to those clinical conditions in which short wave therapy may prove of no value or may be harmful. The contraindications to the use of this therapy are considered at the end of this section.

A fairly complete bibliography and index are included, and this work should serve as a valuable reference to any one employing short wave therapy. The illustrations are numerous and clear.

News and Comment

Central Society for Clinical Research.—The twelfth annual meeting of the Central Society for Clinical Research will be held in Chicago, with headquarters at the Drake Hotel, on Nov. 3 and 4, 1939. Dr. Walter H. Nadler is president; Dr. Charles A. Doan, vice president, and Dr. Lawrence D. Thompson, secretary-treasurer.